ANNALS OF INTERNAL MEDICINE

PUBLISHED MONTHLY BY

The American College of Physicians

VOL. 35 (O.S., Vol. XL) OCTOBER, 1951 NUMBER 4

CONTENTS

Page

New Problems in the Treatment of Infectious Diseases. C. PHILLIP MILLER 763

Preventive Immunization in a National Emergency. R. E. DYER 771

Air Embolism. ARCHIBALD C. COHEN, GEORGE C. GLINSKY, GEORGE E. MARTIN and K. I. FETTERHOFF 779

Gastric Antacid and Anti-Secretory Drugs: A Survey Based Primarily on Their Effects upon Gastric Secretion in Man. JOSEPH B. KIRSNER, WALTER L. PALMER, ERWIN LEVIN and ARTHUR P. KLOTZ 785

A Test for the More Accurate Recognition of Gall-Bladder and Liver Bile during Diagnostic Biliary Drainage. AUGUSTUS A. HALL and JOHN M. MASEN..... 812

Atelectasis of the Right Middle Lobe Resulting from Perforation of Tuberculous Lymph Nodes into Bronchi in Adults. ABRAHAM G. COHEN 820

Hypercholesteremia: An Analysis of 529 Cases and Treatment of 297 by a Low Animal Fat Diet and Desiccated Thyroid Substance. W. W. PRIDDLE 836

The Rationale of Geriatric Medicine. EDWARD STIEGLITZ 848

Therapy of Traumatic Shock. BENJAMIN BURBANK 857

Myocardial Infarction in a Rural Hospital. FRANCIS F. HARRISON 872

Pain in Acute and Chronic Diseases of the Liver. HOWARD P. LEWIS 878

Some Social Implications of Medical Progress. FRANK G. DICKINSON 889

Case Reports:

Sarcoidosis with Fatal Cardiac Involvement. GEORGE C. ADICKES, S. L. ZIMMERMAN and EDWARD S. CARDWELL, JR. 898

Hypoprothrombinemia Due to Dicumarol in a Malingerer. WILLIAM A. STAFNE and ALLAN E. MOE 910

Acute Idiopathic Hemolytic Anemia: Report of a Severe Fatal Case with Immunologic Observations. CHARLES G. CRADDOCK, JR. 912

Severe Spontaneous Hypersensitivity to Heparin. ALEXANDER GOTZ 919

Serum Neuritis. ISIDORE FISCHER 922

A Case of Hand-Schüller-Christian Syndrome Treated with Cortisone. WILLIAM H. BLAHD, MARVIN S. LEVY and SAMUEL H. BASSETT 927

Editorial—Lipids and Arteriosclerosis 938

Reviews 944

College News Notes 949

Subscription per annum, net postpaid, $10.00, United States, Canada, Mexico, Cuba, Canal Zone, Hawaii, Puer Rico, Philippine Islands, Central and South American Countries, and Spain; $11.00, other countries.

Entered as Second Class Matter August 21, 1933, at the Post Office at Lancaster, Pa., under the Act of Mar 3, 1879. Acceptance for mailing at a special rate of postage provided for in the Act of February 28, 19 embodied in paragraph (d-2), section 34.40, P. L. & R. of 1948, authorized October 7, 1936.

ANNALS OF INTERNAL MEDICINE

VOLUME 35 OCTOBER, 1951 NUMBER 4

NEW PROBLEMS IN THE TREATMENT OF INFECTIOUS DISEASES *

By C. PHILLIP MILLER, M.D., F.A.C.P., *Chicago, Illinois*

IT may seem a bit like looking a gift horse in the mouth to speak about problems in the treatment of infection when so many of them have already been solved by the recent developments in chemotherapy, developments unparalleled in the whole history of medicine. Nevertheless, new problems have arisen which deserve our attention.

Time permits consideration of only three, but they are major problems which have recently become the subject of concern among those responsible for the treatment of infection in our hospitals. The first is the rising incidence of infections caused by drug-resistant bacteria; the second, the increased numbers of unusual secondary infections in patients undergoing treatment with antibiotics. The third problem—a very recent one— has to do with the patient's response to infection as it is modified by treatment with ACTH or cortisone.

No attempt will be made to discuss the toxic effect of any of the antibiotics or the allergic manifestations which appear in patients with natural or acquired hypersensitivity to the antibiotics.

THE INCREASING INCIDENCE OF DRUG-RESISTANT INFECTIONS

There can be little doubt that we have begun to encounter an increasing number of drug-resistant infections in our hospitals. In considering this problem one must be careful to distinguish the *natural* from the *acquired* resistance of microörganisms. Natural resistance or susceptibility to the action of each antimicrobial agent varies widely among bacterial species as

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 12, 1951.

From the Department of Medicine and The Institute of Radiobiology and Biophysics, The University of Chicago.

they occur in nature, and within a given species it may vary from strain to strain.

Acquired resistance, on the other hand, results from continued exposure to subinhibitory concentrations of any of the antimicrobial drugs. One can easily demonstrate in the laboratory that susceptible strains of many bacteria develop resistance as they are grown repeatedly in media containing increasing concentrations of an antibiotic. In the case of all of the drugs, with the exception of streptomycin, resistance is acquired slowly, either in vitro or in vivo.[1]

Clinically, therefore, it is only in patients unsuccessfully treated over long periods of time that resistance is acquired during the course of infection. Acute infections caused by bacteria sensitive to the drug employed are brought under control too quickly for resistance to develop.

While our experience with the three new antibiotics— aureomycin, choramphenicol and terramycin—is still limited, it is sufficient to indicate that these drugs follow the pattern of the sulfonamides and penicillin, i.e., resistance to them develops slowly.[1]

The development of resistance is explained by the bacterial geneticists as resulting from the appearance within a bacterial population of drug-resistant variants or mutants which arise by the process of random mutation.[2] In the case of all of the drugs except streptomycin, each mutant is only slightly more resistant than its progenitors. It is for this reason that resistance is acquired so slowly. Streptomycin-resistant mutants, however, may be highly resistant, and their appearance accounts for the rapid increase in streptomycin resistance which occurs in vitro and in vivo.

The rapid development of resistance to streptomycin is a common clinical occurrence, most obvious in infections of the urinary tract. In such cases, treatment with streptomycin, to be successful, must completely eliminate the bacteria within a period of three or four days, or resistance will have developed to such degree as to make further treatment useless.

The foregoing applies only to the ordinary bacteria which multiply rapidly. Microörganisms such as tubercle bacilli, which multiply slowly, require a much longer time to develop resistance, even to streptomycin.

Consideration of a second type of streptomycin-resistant mutant, one which is dependent upon streptomycin for growth, is not pertinent to this discussion because its clinical significance is still uncertain.[3, 4] *

The phenomenon of acquired resistance has been advanced to account for the increasing prevalence of drug-resistant infections. One has but to recall the belief widely held at the time, that the gradual failure of sulfonamide therapy in gonococcal infection was the result of acquired resistance.

It will be remembered that soon after the sulfonamide drugs came into general use, there occurred a marked increase in the percentage of cases of

* Mention should be made of the work of Pratt and Dufrenoy [5] and the recent studies of Garrod,[6] which show that growth of some strains of bacteria may actually be stimulated by appropriate concentrations of penicillin.

acute gonococcal infection which failed to respond to the drug. Moreover, infections which were refractory to treatment were found to be caused by strains of gonococci which, on laboratory test, proved to be resistant to drug, or at least sufficiently resistant to be unaffected by concentrations which could safely be attained in patients.

Either of two explanations of these findings was possible: (a) that individual strains of the gonococcus had each acquired resistance in vivo during exposure to the drug in its host, or (b) that the widespread use of the drug had eliminated many sensitive strains already present. Among a number of observations supporting the latter hypothesis is that of Schmith and Reymann,[7] who found some sulfonamide-resistant strains among 50 old laboratory cultures isolated from patients in the pre-sulfonamide era. Some of those strains were as resistant as any later recovered from infections which failed to respond to sulfonamide therapy.

This demonstration of the preëxistence of resistant strains forces one to the conclusion that widespread treatment with these drugs resulted in the selective elimination of sensitive strains from circulation among the infected population, without affecting the dissemination of naturally resistant strains already present—until the latter became predominant.

Penicillin Resistant Infections: As penicillin has been in use longer than any of the other antibiotics, any change in the response of infection attributable to its administration should have become apparent. Such a change has, in fact, been observed, but not for all bacterial infections. Finland and his co-workers, for example, recently reported that the penicillin sensitivity of pneumococci [8] was not appreciably different for strains isolated before 1945 and since 1948. They did find, however, that among strains of staphylococci [9] there was a striking increase in the percentage of penicillin-resistant ones in recent years.

Mary Barber, the English bacteriologist, was one of the first to call attention to the rising incidence of penicillin-resistant staphylococcal infections in the surgical wards of a London hospital. She found that the percentage of strains of staphylococci which were highly resistant to penicillin increased during the three year period 1946–1948 from 14 per cent to 38 per cent to 59 per cent.[10] She and other British workers [11] have stressed the point that a large proportion of the infections with penicillin-resistant staphylococci seems to have been acquired in hospital.

It should be mentioned that most, if not all, strains of highly resistant staphylococci produce penicillinase.

The experience of Barber in London and of Finland in Boston is not exceptional. Spink [12] has recently called attention to a similar increase at the University of Minnesota Hospitals. Moreover, verbal reports from other workers indicate that the incidence of penicillin-resistant staphylococcal infection is steadily increasing in many places in this country.

It seems probable that we are gradually reducing the numbers of

penicillin-sensitive strains of pathogenic staphylococci by the indiscriminate administration of penicillin, just as we eliminated sulfonamide-sensitive gonococci. Fortunately, most penicillin-resistant staphylococci are sensitive to some other antibiotic or to combinations of them.

Combined therapy with two or more antibiotics has been found to be effective against infections which cannot be controlled by the administration of one alone. It should be mentioned in passing, however, that some recent work of Jawetz [13] has demonstrated that the addition of chloramphenicol or aureomycin to penicillin reduced the effectiveness of the latter in the test tube and also in experimental infections in mice. This inhibition of the action of penicillin could be overcome by using greater concentrations of penicillin.

Importance of Bacteriologic Diagnosis: Now that we have a considerable choice of antibiotics at our disposal, it is more important than ever to select the one most effective for the treatment of any given infection. It is essential, therefore, to establish a bacteriologic diagnosis, which, in turn, requires that appropriate cultures be made before treatment is initiated.

It is now possible to test the sensitivity of bacteria to the various antibiotics quite easily by means of small paper discs impregnated with different concentrations of the drug. The culture to be tested is inoculated on the surface of an agar plate, and a set of discs is placed over the inoculum. After incubation, the zones of inhibition about each disc indicate the relative susceptibility of the strain to each antibiotic used. The method is sufficiently accurate for all practical purposes. It is a simple and rapid means of determining the sensitivity or resistance of a particular strain of bacteria whenever that information is needed for the selection of the most effective antimicrobial drug.

Complicating Infections Resulting From Antibiotic Therapy

Another problem which has resulted from the widespread use of antibiotics is the occurrence during treatment of unexpected secondary infections with bacterial species insensitive to the drug being administered. Such infections are often caused by microörganisms usually regarded as nonpathogenic. They are particularly apt to arise in the respiratory tract in children, or in old people suffering from debilitating disease. Weinstein [14] a few years ago reported a series of such instances and emphasized the importance of watching for them in patients receiving antibiotic therapy.

This point is well illustrated in the case of a surgical patient recently observed to whom it had been necessary to administer several antibiotics. She complained at the time of a sore throat and, on examination, her entire oropharynx was found to be acutely inflamed. Cultures of her throat and mouth contained nothing but *Pseudomonas pyocyanea,* in pure culture.

Woods [15] has recently called attention to the occurrence of monilial infection of the throat in patients under treatment with antibiotics. Not all such infections give rise to symptoms. Miller and Bohnhoff [16] demonstrated

an unusually high incidence of these yeastlike microörganisms in the throats of patients undergoing treatment with streptomycin. In none of these patients had their presence given rise to symptoms.

The pathogenesis of such infections is still obscure because we have too little basic information about the interrelationships of the various microorganisms which compose the normal flora of the throat. It is evident, however, that massive doses of penicillin, for instance, administered for the treatment of lobar pneumonia, not only eliminate the pneumococci from the lung but the gram-positive cocci from the throat as well. Lipman, Coss and Boots [17] showed some years ago that prolonged administration of penicillin to normal subjects resulted in a replacement of the predominantly gram-positive flora of the throat by gram-negative bacteria.

This is the sort of change which the ecologists describe as a disturbance or upset in the balance of nature.

The cases in which an antibiotic disturbs the normal flora of the throat in such way as to allow one microörganism to become predominant are particularly interesting and are clinically important when that microörganism happens to be pathogenic.

The normal flora commonly include a few pathogenic members which are held down to inconsequential numbers by the body's natural defenses against infection. It is possible, however, that the presence of other members of the bacterial population plays a rôle in maintaining a state of healthy equilibrium. This restraining action is ascribed to bacterial antagonism.

The problem of bacterial antagonisms has been investigated for many years by bacteriologists, particularly those interested in the microbiology of soil and sewage.[18] The bacterial antagonisms involved in the maintenance of the normal flora of the throat are difficult problems to study experimentally. Thompson and his co-workers [19] have shown that the inhibitory action of human saliva on diphtheria bacilli is due to the presence of *Streptococcus viridans*, and that this microörganism accomplishes its antagonistic effect by its production of hydrogen peroxide.

In the case of the intestinal flora, we have some insight into the mechanisms involved. The work of Gratia and Fredericq [20] in Belgium and of Heatley and Florey [20] in England and of Halbert [21] in this country has shown that many strains of coliform bacilli elaborate an antibiotic effective against other bacteria.

An unexpected result was recently encountered in our studies on the treatment of mice exposed to ionizing radiation. It had been found that the administration of large doses of streptomycin caused a significant reduction in mortality by preventing the development of septicemia resulting from invasion of the blood stream by bacteria from the intestinal tract.[22] When mice were given very small doses of streptomycin by mouth, however, the development of septicemia was hastened.[23]

This result presumably was brought about by some disadvantageous

change in the bacterial population through the elimination of those members of the intestinal flora highly sensitive to streptomycin.

Infection Following Treatment with ACTH and Cortisone

The third problem to be considered is the effect of ACTH and cortisone on infection. The problems already discussed had to do with the effect of therapy on the bacterial parasite, while this last problem derives from an interference with the natural defense of the host against bacterial infection.

Beck and his co-workers [24] have reported a case of pneumococcal peritonitis which occurred in a patient under treatment with ACTH, and one hears verbal reports of cases of generalized infection which have occurred in patients under treatment with these drugs. Such infections are very serious complications because they are not accompanied by fever and the customary symptoms and signs of infection, and for this reason may get out of hand before they are recognized.

Mogabgab and Thomas [25] have shown that the intracutaneous injection of hemolytic streptococci into cortisone-treated rabbits results in a fatal septicemia, although it produces in control rabbits only a small cutaneous infection. In normal animals, the acute inflammatory reaction at the site of inoculation keeps the infection localized, but treatment with cortisone suppresses this response and permits the infection to become generalized.

Kass and his co-workers [26] found that in mice passively immunized with antipneumococcal serum, treatment with cortisone increased the mortality from pneumococcal infection.

Berlin and Hawk [27] have observed that normal mice treated daily with large doses of cortisone died within three weeks with multiple abscesses in various viscera and septicemia caused by bacteria from the respiratory and intestinal tracts. Prolonged treatment with large doses of ACTH, on the other hand, did not produce this effect in mice.

Summary

Among the problems which confront us in the treatment of infections today, the following seem to be the most important:

First is the increasing prevalence of infections caused by bacteria resistant to our present antibiotic drugs. This increase has not occurred in all bacterial infections. The most striking and most disturbing is the rising incidence of penicillin-resistant staphylococcal infections. This increase is thought to be due to the gradual reduction in numbers of naturally sensitive strains, rather than to the development of acquired resistance.

A second problem is the occasional occurrence during antibiotic therapy of complicating infections caused by bacteria insensitive to the antibiotic being used, sometimes by microörganisms usually regarded as nonpathogenic. When such infections begin, for example, in the pharynx, they may result

from a change in the bacterial flora of the throat, that is to say, from a disturbance of the equilibrium maintained by the bacterial antagonisms within the normal flora.

Finally, infection may become a serious complication during treatment with ACTH or cortisone, presumably because these drugs interfere with the host's defensive response to bacterial invasion.

BIBLIOGRAPHY

1. (a) Garrod, L. P.: Acquired bacterial resistance to chemotherapeutic agents, Bull. Hyg. **25**: 539, 1950.
   (b) Miller, C. P., and Bohnhoff, M.: The development of bacterial resistance to chemotherapeutic agents, Ann. Rev. Microbiol. **4**: 201, 1950.
2. Demerec, M.: Production of staphylococcus strains resistant to various concentrations of penicillin, Proc. Nat. Acad. Sc. **31**: 16, 1945.
3. Miller, C. P., and Bohnhoff, M.: Two streptomycin-resistant variants of meningococcus, J. Bact. **54**: 467, 1947.
4. Spendlove, G. A., Cummings, M. M., Fackler, W. B., Jr., and Michael, M., Jr.: Enhancement of growth of a strain of *Mycobacterium tuberculosis* (var. hominis) by streptomycin, Pub. Health Rep. **63**: 1177, 1948.
5. Pratt, R., and Dufrenoy, J.: Antibiotics, 1949, J. B. Lippincott Co., Philadelphia.
6. Garrod, L. P.: The reactions of bacteria to chemotherapeutic agents, Brit. M. J. **1**: 205, 1951.
7. Schmith, K., and Reymann, F. E.: Experimentelle og kliniske Undersøgelser over Gonococcus Folsomhed overfor Sulfapyridin, Nord. med. tidskr. **8**: 2493, 1940.
8. Jackson, G. B., Gocke, T. M., Wilcox, C., and Finland, M.: In vitro susceptibility of pneumococcus to seven antibiotics, Am. J. Clin. Path. **20**: 218, 1950.
9. Finland, M., Frank, P. F., and Wilcox, C.: In vitro susceptibility of pathogenic staphylococci to seven antibiotics, Am. J. Clin. Path. **20**: 325, 1950.
10. Barber, M., and Rozwadowska-Dowzenko, M.: Infection by penicillin-resistant staphylococci, Lancet **2**: 641, 1948.
11. Forbes, G. B.: Infection with penicillin-resistant staphylococci in hospital and general practice, Brit. M. J. **2**: 569, 1949.
    Rountree, P. M., and Thompson, E. F.: Incidence of penicillin-resistant and streptomycin-resistant staphylococci in a hospital, Lancet **2**: 501, 1949.
12. (a) Spink, W. W.: Clinical and biologic significance of penicillin-resistant staphylococci, including observations with streptomycin, aureomycin, chloramphenicol and terramycin, J. Lab. and Clin. Med. **37**: 278, 1951.
    (b) Nichols, D. R., and Needham, G. M.: Aureomycin in the treatment of penicillin resistant staphylococcic bacteremia, Proc. Staff Meet., Mayo Clin. **24**: 309, 1949.
    (c) Beigelman, P. M., and Rantz, L. A.: The clinical importance of coagulase-positive, penicillin-resistant *Staphylococcus aureus,* New England J. Med. **242**: 353, 1950.
13. (a) Jawetz, E., and Speck, R. S.: Joint action of penicillin with chloramphenicol on an experimental streptococcal infection of mice, Proc. Soc. Exper. Biol. and Med. **74**: 93, 1950.
    (b) Jawetz, E., Gunnison, J. B., Speck, R. S., and Coleman, V. R.: Studies on antibiotic synergism and antagonism; the interference of chloramphenicol with the action of penicillin, Arch. Int. Med. **87**: 349, 1951.
14. Weinstein, L.: The spontaneous occurrence of new bacterial infections during the course of treatment with streptomycin or penicillin, Am. J. M. Sc. **214**: 56, 1947.
15. Woods, J. W., Manning, I. H., and Patterson, C. N.: Monilial infections complicating the therapeutic use of antibiotics, J. A. M. A. **145**: 207, 1951.

16. Miller, C. P., and Bohnhoff, M.: Effect of streptomycin therapy on the bacterial flora of the throat, Am. J. Med. **6**: 417, 1949.
17. Lipman, M. O., Coss, J. A., and Boots, R. H.: Changes in the bacterial flora of the throat and intestinal tract during prolonged oral administration of penicillin, Am. J. Med. **4**: 702, 1948.
18. Waksman, S. A.: Microbial antagonisms and antibiotic substances, 1945, The Commonwealth Fund, New York.
19. Thompson, R., and Johnson, A.: The inhibitory action of saliva on the diphtheria bacillus: hydrogen peroxide, the inhibitory agent produced by salivary streptococci, J. Infect. Dis. **88**: 81, 1951.
20. Florey, H. W., Chain, E., Heatley, N. G., Jennings, M. A., Sanders, A. G., Abraham, E. P., and Florey, M. E.: Antibiotics, vol. 1, 1949, Oxford University Press, London.
21. Halbert, S. P.: The relation of antagonistic coliform organisms to Shigella infections, II. Observations in acute infections, J. Immunol. **60**: 359, 1948.
22. Miller, C. P., Hammond, C. W., and Tompkins, M.: Reduction of mortality from x-radiation by treatment with antibiotics, Science **3**: 719, 1950.
23. Miller, C. P., and Bohnhoff, M.: Unpublished experiments.
24. Beck, J. C., Browne, J. S. L., Johnson, L. G., Kennedy, B. J., and MacKenzie, D. W.: Occurrence of peritonitis during ACTH administration, Canad. M. A. J. **62**: 423, 1950.
25. Mogabgab, W. J., and Thomas, L.: Effects of cortisone on experimental infection with Group A streptococci in rabbits, Central Soc. Clin. Inv. **23**: (Nov.) 1950.
26. Kass, E. H., Ingbar, S. H., Lundgren, M. M., and Finland, M.: The effect of ACTH and cortisone on pneumococcal and influenza viral infection in the white mouse, J. Lab. and Clin. Med. **37**: 780, 1951.
27. Berlin, B. S., and Hawk, W. D.: Personal communication to the author.

PREVENTIVE IMMUNIZATION IN A NATIONAL EMERGENCY *

By R. E. Dyer, M.D., *Emory University, Georgia*

The Board of Regents of the American College of Physicians has conferred a great honor upon me in selecting me as the James D. Bruce Memorial lecturer in preventive medicine. It is with a feeling of great pride that I accept this honor. James D. Bruce was born in 1872 and died in 1946. During his early life, necessity for preventive medicine and specific immunizing procedures in a national emergency was forcibly emphasized by the losses suffered by our troops in the Spanish American War, particularly from typhoid fever and yellow fever. The beginning of modern preventive medicine and the stimulation of research which has developed with ever increasing speed began with Koch and Pasteur, when Dr. Bruce was still a young man. The results of research on the etiology of infectious diseases and methods of control, including specific immunization procedures, together with the development of better clinical care and treatment, have resulted, as we all know, in an increase in our life expectancy at birth from 35 years in the time of our Revolutionary War to 47 at the time of the Spanish American War, and now almost to the Biblical span of three-score and ten. However, many problems in infectious diseases remain to be solved. For the purpose of this lecture we will confine our thoughts to present specific immunization procedures in the fields of infectious diseases with reference to both military and civilian personnel.

In past war, because of our geographic isolation, we did not have to consider the problem of protecting civilians against infectious agents to the same extent I fear we shall be compelled to in the future. In World War I and World War II our increased efforts to protect civilians were designed particularly to reduce the risk of infection among our troops resulting from exposure to infected civilians while in training in this country and in service abroad. Since a future war might conceivably be fought in part within our boundaries, the protection of the civilian population becomes much more urgent. In addition to the danger of disease casualties which might well follow the disruption of sanitary and other facilities, following an actual bombing, whether it be by an atom bomb or by the type of bombs now in use, we have the danger of the use of biologic agents as weapons. The use of such agents might well be more disastrous to our civilians than to our armed forces. The diseases which have been of greatest military importance are those of a communicable nature which occur in epidemics, whether the method of communication is by person-to-person contact, through the agency

* James D. Bruce Memorial Lecture, presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 9, 1951.

of food and water, or by reason of insect transmission. Prior to World War II the diseases which played the greatest havoc among armies throughout the world and throughout the centuries have been typhus, typhoid, dysentery, smallpox, tetanus, the venereal diseases, influenza, pneumonia and, in the Spanish American War, yellow fever. Measles, mumps and meningitis also have been of importance, particularly in our training camps in World War I. The common respiratory diseases have always been of great importance among troops. The communicable diseases already mentioned are, with the exception of yellow fever, diseases of the temperate zone. We have been particularly concerned with these diseases because the great wars in which we and our ancestors have been engaged for centuries have been fought in the temperate zone. The field of battle in World War II included not only the temperate zone but also the tropical and subtropical zones. A future war may include the arctic regions. The activities of our troops in World War II in the tropics and subtropics made the so-called tropical diseases of greater importance, particularly malaria as an actuality and yellow fever as a threat. In addition to these two, we had to attempt through research to work out better methods of prevention and treatment of such diseases as plague, cholera, tsutsugamushi, dengue, filariasis, schistosomiasis and others.

In World War I we had effective vaccines against such diseases as smallpox, typhoid and diphtheria but none against dysentery, tetanus, typhus, yellow fever, influenza, cholera, plague, meningitis, pneumonia, mumps, measles, Q fever and others. Research work through the years between the two world wars resulted in the improvement of some of the vaccines already in use, and the development of new vaccines against certain of the other diseases mentioned. The results of research in specific therapy in the past few years have made possible the prevention of deaths and the lessening of time off duty occasioned in the past by a number of diseases.

Smallpox, against which we have an effective vaccine, is not a disease of great military importance as far as our troops are concerned, since the use of the vaccine has practically eliminated it as a casualty among our armed forces. Smallpox, however, could be a threat to our civilian population, since too large a number of our civilians have not been adequately protected by vaccination. The threat of smallpox to our civilian population in a national emergency will be referred to later.

Typhoid fever was one of the scourges of our army in the Spanish American War, since no vaccination was available at that time and the sanitary facilities were quite inadequate. The method of protecting troops against typhoid fever by vaccine was first used extensively by the British in the Boer War. Our use of the vaccine to protect troops began in 1908. Between that time and the onset of World War I, some modifications were made in the technics of preparing the vaccine, but essentially the immunizing value remained the same. In the years between the two world wars, im-

provement in the value of this vaccine was made by research carried on by the staff of the Army Medical School. Sanitary care and the use of the vaccine held the typhoid fever morbidity rate in our army in the last war to .03 per thousand.

In diphtheria progress in immunizing procedures was made in the period between the two wars. Diphtheria toxoid, prepared by the addition of formalin to the toxin, was discovered in 1921. This toxoid, now used extensively in protection of children, has gone a long way in the control of this disease.

Following the discovery of diphtheria toxoid, the same method was used to prepare a similar product from tetanus toxin. Our armed forces were routinely inoculated with tetanus toxoid at time of their entry into the service during World War II, and an additional booster dose was given at the time of injury, with the almost complete protection of all troops. The few cases of tetanus which occurred among our wounded were in general explained by the failure of some individuals to receive the initial inoculation or a stimulating dose at the time the wound was received. This immunization procedure against tetanus, now practiced so generally in the immunization of children, promises to do as much eventually in reducing the incidence of tetanus in the civilian population as diphtheria toxoid has accomplished.

Two new vaccines were elaborated in the years between World Wars I and II, yellow fever vaccine and typhus vaccine. It is difficult for us to realize what a dread threat yellow fever was to the population in the southern part of this country prior to the discovery of the method of transmission and the development of measures of mosquito control. The methods of controlling mosquitoes have proved adequate for the protection of our resident population since the first few years of this century. Such measures, however, would be of little value for the protection of our armed forces employed in areas where yellow fever is endemic. Such measures could probably be used effectively should yellow fever again be introduced into this country either accidentally or intentionally. At the time of a national emergency, such measures would consume manpower, time otherwise devoted to the production of materials, hospital facilities and money.

The discovery of a vaccine for the prevention of yellow fever is one of the outstanding examples of the progress made in specific immunization. An attack of yellow fever gives a permanent immunity in practically all individuals. The disease is caused by a virus however, and, as in smallpox, all attempts to produce an effective vaccine by the use of killed virus resulted in failure. Studies made in an attempt to reduce the virulence of the virus —by repeated passage through Rhesus monkeys, then in embryonic mouse tissue culture, and finally in the living chick-embryo—resulted in the development of an efficient vaccine. The results following the use of this vaccine in Brazil in 1937 and 1938 and later for the protection of our troops,

and subsequent testing of the protective value of the serum of immunized individuals, have demonstrated its efficiency. How long the immunity lasts is not known. Possibly the duration of this artificially produced immunity may be at least equal to the immunity produced by smallpox vaccination. As far as the author knows, no case of yellow fever occurred among our troops during the African campaign of World War II. Should yellow fever be introduced into this country in a national emergency, this vaccine, together with the mosquito control measures referred to above, will effectively control the disease. It should not be forgotten, however, that the emergency vaccination of large numbers of individuals would take time and manpower, with a corresponding decrease in our production of materials essential for defense.

Epidemic typhus is one of the great military diseases of history, having taken an effective and at times a decisive part in many military campaigns. To cite only one, it may be recalled that typhus has been credited with having killed more of Napoleon's troops on his retreat from the disastrous Russian campaign than did cold and starvation. Typhus has also caused severe epidemics among civilian populations. Again Russia may be referred to, since it is estimated that two or three million deaths occurred in Russia from typhus during the years between 1917 and 1923. Little is known about the occurrence of typhus in Russia during and following World War II. Epidemic typhus has been introduced into this country from time to time in the past, but it has never reached epidemic proportions. Economic conditions were then, as now, unfavorable for the spread of this louse-borne disease. The development of typhus vaccine occurred in the years immediately preceding the onset of World War II and in the early years when we were involved in actual conflict.

Two successful methods of production of typhus vaccine were developed. One of these utilized the Rickettsiae grown in the yolk sac of the developing chick embryo, whereas in the second the Rickettsiae were harvested from the lungs of rats or rabbits which had been inoculated intranasally with infected material. The chick embryo yolk vaccine, developed in this country, was easily made in large quantities and was used to vaccinate the members of our armed forces. Our own troops encountered an outbreak of typhus during the attack on Naples during the last war. Our troops engaged in that encounter had been protected by typhus vaccine and, following the use of DDT in Naples, the epidemic disappeared. There was no death from typhus in World War II among our vaccinated troops, despite exposure in North Africa, Italy and Germany. The incidence of cases was extremely low and the individual attacks were mild.

Bubonic plague is a disease of great importance in certain areas of the world, such as China, India, the East Indies and Burma. With the situation in the world as it is today, the necessity for an active immunizing agent for the protection of our troops becomes much more apparent. Two types

of vaccines against plague have been used for many years, one containing living organisms of reduced virulence, the second containing heat-killed bacilli. During World War II research was aimed at improving the killed vaccine by the use of formalin instead of heat. The studies made to date indicate that the formalin-killed vaccine produces as high a degree of immunity in experimental animals and in tests on a few human volunteers as does the vaccine made from the living avirulent strains. Although data collected through the years indicate that these plague vaccines reduce the mortality among individuals who subsequently contract plague, the reduction of morbidity is still an open question.

Cholera, like plague, may present a more serious problem to our armed forces in the future than it has in the past. Before the last war, heat-killed cholera vaccine had been extensively used in Japan and India, with apparently a reduction in the morbidity and mortality rates. During that war, studies were set up which undertook the examination of many strains of cholera vibrios to select the one most efficient for use in a vaccine and for the improvement of methods of manufacture. Experimental evidence in these studies, including a small series of trials on human volunteers, indicates that this killed vaccine may have value. No field trials have been completed at the present.

Bacillary dysentery has been one of the great problems among troops of all nations. Great effort has been expended to develop an effective vaccine against this disease but without much success.

The history of influenza at the close of World War I has placed this disease high on the list of vaccine development programs. Vaccines have been prepared which show protection against the strains of virus employed in their manufacture. Whether any of those now used would produce a vaccine which would be of value should a strain similar to that of 1918 again appear is questionable. Active agents for immunization have also been prepared for protection against whooping cough, mumps and Q fever. No extensive field trials have been made in mumps and Q fever vaccines, but the evidence collected indicates that these two vaccines are of definite value.

As reviewed above, we have vaccines of proved value against certain diseases to which our troops will be exposed in war, other vaccines of less value, and no vaccines against many other infections. Our troops are immunized with the various vaccines at time of entry into the service and have little to fear from smallpox, typhus, tetanus and yellow fever. On the other hand, our civilian population is on the whole poorly immunized against these diseases. As stated before, we can control certain epidemics in our civilian population in time of national emergency, but the cost in time, manpower and money and the accompanying hysteria would be a severe handicap to our war time production. As an example of this, the experience of New York City may be cited.

A salesman returned from Mexico to New York City in 1947, traveling

by bus. He died of smallpox in New York. Through contact with this patient during his fatal illness and secondary contacts, some 11 cases developed. Because of the definite possibility of the development of an epidemic in New York, steps were taken by the health authorities to carry out a wholesale smallpox vaccination program which resulted in the vaccination of more than 7,000,000 individuals. This program placed a heavy strain on the health authorities and the medical personnel of the city, consumed an enormous amount of vaccine, cost much in time and manpower, and millions of dollars, and was accompanied by widespread popular hysteria in other cities of the North Atlantic Coast. This case of smallpox from Mexico, an accidental introduction of the disease, serves as a good illustration of the havoc that threat of an epidemic will cause. This leads us to the much discussed subject of biologic warfare.

Smallpox is not a good example of a probable biological weapon, but it does serve to stress the fact that our civilian population is very inadequately protected by preventive immunization against this and the other diseases against which our troops have been immunized. At the outset, biological warfare may be defined as "the intentional use of living disease agents, or their toxic products, for the purpose of producing disease or death in man, animals or crops." The statements that have been made in the past about the danger of an enemy's using biological agents and their toxins have varied from estimating the threat of this form of warfare as being as great as or greater than the threat of the atomic bomb, to the other extreme, where the subject is dismissed as of no importance. The true picture lies between these extremes. Biological warfare is a definite threat to our population, through direct attacks on the human population, military and civilian, and indirect attacks through destruction of man's food supply by the use of available agents infectious to animals and crops. Indeed, the danger of initiating an epidemic in animals or spreading disease in certain crops is greater than the danger of the establishment of an epidemic in our human population. Spreading infection among our livestock, cattle, swine, sheep and fowl would not only seriously endanger our food supply but would also seriously limit our production of such preparations as insulin and adrenalin, to cite only two examples. It would be natural to assume that agents selected by an enemy for use against animals and poultry would be agents that are foreign to this country, against which no immunity has been built up among our livestock. Examples of such agents which an enemy might select for use in this particular field are foot-and-mouth disease, rinderpest, fowl pest, and foreign types of Newcastle disease. In regard to the diseases of plants and destruction caused by insect pests, it should be noted that at the present time billions of dollars are lost from these causes each year in this country. The author is not qualified to discuss the specific immunization against various species of livestock diseases.

In initiating biological warfare, delay until actual hostilities have begun

might not appeal to an enemy. An enemy might well prefer to introduce biological agents against man and his food supply prior to actual war to hamper us in our preparations for conflict. With reference to the use of biological agents against the human population, I would like to quote excerpts from a recent publication distributed by the Federal Civil Defense Administration: "A determined and resourceful enemy could employ the agents of biological warfare against us effectively. Such agents might be delivered by sabotage before or after open war, or as a part of an overt attack. Attempt to incapacitate a limited number of selected individuals in order to delay military or industrial mobilization and production before the occurrence of open warfare. Use biological warfare in order to lower efficiency, production and morale." The agents that have been given as examples are the viruses, such as psittacosis and influenza, rickettsial diseases such as typhus, and Q fever; bacterial infections, as typhoid, cholera, plague and tularemia; fungi, as histoplasma or coccidioides, and toxins, for example, that produced by *Clostridium botulinum*. Many of these pathogens are quite stable, resisting heat, drying and sunlight. The agents cited above, as well as many others, can be produced in large quantities and can be easily distributed by air and water, or by food. By air a rickettsia, or, more probably, a mixture of two or three species of rickettsiae, could be disseminated by aerial bombs; or, without bombs, infected aerosols could be released into the air from planes, or ground devices or, depending on favorable air currents, from submarines lying off our large coastal cities. The probable effectiveness of such measures may be emphasized by reference to the Donora smog episode in 1948 and to the fact that other of our large industrial centers are now plagued by smog. Such aerosols could also be introduced into closed ventilating systems of munitions plants, auditoriums, legislative halls, executive offices of our armed forces, hotels and other buildings. That a very high percentage of those exposed to aerosols infected with certain materials will become ill the author has no doubt. This conviction is based on many years' experience with these diseases, during which there occurred two outbreaks of Q fever totalling some 60 cases, 11 cases in one outbreak of psittacosis, and 40 cases of typhus over several years. These outbreaks, as well as occasional cases of tularemia, brucellosis, tsutsugamushi and other infections, occurred in one laboratory. No adequate explanation could be reached as to the mode of transmission save that the infectious agents were airborne. Two cases of tsutsugamushi, one of which ended fatally, were definitely traced to the operation of a Waring blender in the room where the two men were working. A second instance may be cited in which typhus fever occurred in an unvaccinated scientist 12 days after he spent 10 or 15 minutes in a room where a Waring blender containing infectious typhus material had been in operation for a short time. The operation had been discontinued a half-hour before the scientist entered the room. Infectious material of this sort could easily be blown into the air intake of ventilating

systems by a small hand spray-gun, or by mechanical equipment which could easily be carried in a small suitcase. In the case of water and food, different but effective methods could be used with comparable results by the introduction of an agent or agents (bacteria or their toxins) into city water mains or the mains supplying the large industrial plants engaged in war munitions production. Many such infections, whether water borne or air borne, would probably not spread to secondary contacts. One of the important things about the use of such agents in sabotage, whether the infection be produced by bacteria, viruses or rickettsiae, is the delay following the release of the infectious particles before illness occurs. Cases would not show signs of illness until the incubation period had passed. In most instances this would be one to two weeks. In other words, one very small group of saboteurs could distribute the infective aerosols in several locations, in one city or several cities, destroy the equipment used for dissemination, and get safely out of the country before any suspicions were aroused by the occurrence of multiple cases of one or more diseases. It should be pointed out that an agent, to be effective, need not produce a high fatality rate. Illness requiring absence from work, medical care, and insuring production of hysteria among the population, might well prove more effective than one causing a large number of deaths.

As cited above, against some of the agents that might be used in biological warfare we have certain immunizations of proved value with which our troops will be and are being protected. However, our civilian population is not adequately protected against these agents. The question of the protection of our civilians by mass immunizations using our present vaccines must be given consideration. Such consideration should be given to the question of whether we should protect our civilians by mass immunization generally, or by applying this procedure only to our large population centers, or to key personnel in other localities. Should this procedure be deemed unnecessary at this time, steps should be taken to insure an adequate supply of vaccine on short notice.

To summarize briefly, it may be stated that much progress has been made in preventive medicine and the development of preventive immunizations in the past 75 years. Our troops are adequately protected against those diseases against which preventive vaccines have been developed. This statement does not apply to our civilian population. Much research remains to be done on diseases the prevention of which remains unsolved. The increasing rate of progress in preventive measures in past years leads us to believe that even greater progress will be made in the future.

AIR EMBOLISM *

By Archibald C. Cohen, George C. Glinsky, *Butler, Pennsylvania,*
George E. Martin, F.A.C.P., and K. I. Fetterhoff,
Pittsburgh, Pennsylvania

There are two types of air embolism, differing from each other in the site of entrance of the air, its distribution within the blood vessels, and its effects.[1]

In arterial embolism, the air enters a pulmonary vein, passes through the left ventricle and reaches systemic arteries on the upper part of the body. A small amount of air can block an important artery completely; so the injection of only a few cubic centimeters of air may be fatal if it reaches a cerebral or coronary artery. If air enters the cerebral circulation—this is common if the head is higher than the aortic arch—neurologic manifestations such as aphasia, blindness, hemiplegia or convulsions may result. In such cases, ophthalmoscopic examination may reveal air bubbles in the retinal arteries. A marbled appearance of the skin suggests air in the superficial vessels, and is often found in the superiorly located portions of the body. A small incision in the skin over the upper part of the body may show that the blood contains air bubbles. This is known as "air bleeding," and is proof of the existence of arterial air embolism.[2] Myocardial infarction has been demonstrated by electrocardiography [3] and at post mortem.[4]

Arterial air embolism is usually a complication of artificial pneumothorax, thoracentesis or thoracic surgery. Air is either injected accidentally in the course of the procedure, or venous pathways are opened up and air is sucked into them before clotting can occur. It can easily be understood how this could happen: as the pressure in the veins is below atmospheric and the pressure in the air-passages is atmospheric, air would easily pass into the veins if the wall of a vein is opened. Arterial air embolism also occurs regularly as a part of caisson disease.

The treatment of arterial air embolism is postural and supportive. The head should be lowered at once. This will not prevent emboli from reaching the coronary circulation, and will not dislodge air bubbles already present in the cerebral circulation, but it will prevent any more air from reaching the brain. External heat should be applied if necessary, treatment for shock should be given if the patient goes into shock, and adequate control of the patient should be provided if there are convulsions.

* Received for publication March 15, 1950.
Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.
From the Veterans Administration Hospital, Butler, Pennsylvania, and the City Tuberculosis Hospital, Pittsburgh, Pennsylvania.

Case Reports

Case 1. This patient was a 22 year old Negro male with bilateral pulmonary tuberculosis and a small cavity on the left. He was admitted to the hospital on March 3, 1946, with a history of having been sick for over two years. He had felt weak, lost 32 pounds in weight, and had repeatedly experienced pain on the left side. There had been no hemoptysis. Sputum was consistently positive for tubercle bacilli, and temperature on admission was 102° F. He was kept in bed, and in the next two months his temperature gradually subsided. Roentgen-ray failed to show improvement, however, so it was decided to attempt pneumothorax on the left. On May 7, 1946, pneumothorax was attempted at three different locations on the left; no manometric readings were obtained, and no air was injected. The patient was allowed to sit up, preparatory to returning him to his ward. While lying down he had been comfortable. As soon as he sat up he complained that he felt "funny." At once he was replaced in the horizontal position and the head of the table was lowered. However, he lost consciousness within a minute or two, had generalized convulsions, and lost sphincter control; breathing became stertorous, and in less than 10 minutes from the time he sat up he was dead. Autopsy permission was not obtained.

In this case no air was injected. The symptoms can be readily explained on the basis of air embolism of the cerebral arteries, though absolute proof of the diagnosis could not be obtained. As to how air entered the circulation, it may be speculated that the needle punctured the lung, making an opening in a branch of the pulmonary vein. Into this opening air might easily flow, since the pressure of the air in the lung was atmospheric and the pressure in the vein was below atmospheric. Death might have been prevented if the patient had been kept horizontal until the needle-puncture closed.

Case 2. This patient was a 27 year old white woman with an extensive, almost exclusively left-sided tuberculous lesion with multiple cavities. She was admitted to the hospital on January 9, 1940. Onset of disease was only about six months previously. Temperature was below 100° F.; sputum was positive. Pneumothorax on the left was instituted in February, 1940. An extensive but ineffective pneumothorax was obtained, the upper third of the lung being connected to the chest wall by many adhesions and the cavities remaining open. Pneumothorax was, however, continued pending thoracoscopy. A refill was given on March 2, 1940; the initial pressure was minus 5, minus 1 cm. of water, and an injection of 300 c.c. of air was given. Suddenly the patient complained of spots before her eyes. The needle was at once withdrawn and the head of the table was lowered. However, in rapid succession she complained of dimness of vision, of total blindness, and of generalized headaches. She became very apprehensive, but did not lose consciousness or develop convulsions or loss of sphincter control. Her blood pressure, previously normal, rose to 168 mm. Hg systolic and 96 mm. diastolic. Ophthalmoscopic examination showed bubbles in both retinal vessels. She was returned to bed on an inclined stretcher, her head being kept low. She was confined to bed with the foot of the bed elevated for 48 hours. Otherwise she received only symptomatic treatment. Some degree of vision was restored in less than an hour, and vision was entirely normal next morning. The headache persisted for several weeks but eventually cleared up. Pneumothorax was discontinued.

Two possibilities were considered as to the origin of this cerebral embolism. Perhaps the operator's needle was allowed to slip inward during the injection of air, so that air was actually injected into a pulmonary vein; or perhaps an adhesion ruptured, laying open a vein into which air could be sucked at each inspiration.

Case 3. This patient was a 49 year old white man who was admitted to the hospital on March 10, 1948. Onset of disease was six months previously, hemoptysis four months previously. As there was no improvement on bed rest, a right phrenic crush was done on June 17, 1948, and pneumoperitoneum was instituted on June 21, 1948. On January 25, 1949, following the uneventful administration of 600 c.c. of air into the peritoneal cavity, patient got off the table and immediately collapsed to the floor and had a period of apnea lasting about 45 seconds, with marked cyanosis of the face and neck, followed by a short, generalized convulsion and relaxation of sphincters. Pulse was rapid and thready. He was placed in the left lateral position, head down. Breathing was resumed and the color became normal, and within a minute or two the pulse became full again. There was a marbled appearance of the skin over the right lateral aspect of the thorax. He was returned to bed in Trendelenburg's position and kept in that position for 10 hours. Pupils were dilated. Eye grounds were normal. There was much motor restlessness of the left side of the body, as well as paralysis of the right upper and lower extremities. Abdominal and cremasteric reflexes were absent. The electrocardiogram was normal. He remained semistuporous for an hour. On recovering consciousness, he complained of blindness (could distinguish between light and dark, but could not count fingers) and had tremors of his right arm. He complained also of severe generalized headache, requiring demerol for 36 hours for its control. He was considered critically ill, and his family was notified. On the second day he still had severe headache and there was twitching of the right forearm and hand, but vision was improving and neurologic examination was negative. On the third day headache had disappeared, vision was normal, there was no more twitching, and neurologic examination was negative. He had no further difficulty, and pneumoperitoneum has been continued uneventfully to the present time.

Case 4. This patient, a 20 year old white man, was admitted to the hospital in June, 1948. Pneumoperitoneum was begun on June 25, 1948. On November 19, 1948, he received 600 c.c. of air into the peritoneal cavity; initial pressure 0 plus 1; air was aspirated readily; final pressure plus 3 plus 4 cm. of water. Following this refill he had no complaints but got off the table, walked a few steps and began to put on his bathrobe. He then staggered and turned ashen, said he felt dizzy, and slumped to the floor. The entire time involved was not more than 60 seconds. He immediately lost consciousness, frothed at the mouth and had generalized convulsive twitchings. He was placed in left lateral position and his head was kept low. In about 10 minutes consciousness began gradually to return; he was sent back to the ward and put to bed in Trendelenburg's position. His pulse was of good quality throughout, but rapid (140 per minute). On his return to the ward, blood pressure was 130 mm. Hg systolic and 94 mm. diastolic, and ophthalmoscopic examination was negative. He complained of dizziness and had an involuntary bowel movement; dizziness and slight cyanosis of lips and fingertips persisted for 30 minutes. Two and a half hours after onset he had slight headache and nausea, but no vomiting. From this time on he felt well. Pneumoperitoneum refills were continued uneventfully.

Cases 3 and 4 pose an interesting question: How can air injected into the peritoneal cavity find its way into the cerebral circulation, as apparently

happened in these cases? It is difficult to explain how it gets into the circulation at all, especially in old-established cases of pneumoperitoneum like these. And even assuming that, by an error in technic, air is injected into the circulation, it is hard to see how it could get into the cerebral circulation. If injected into an artery it should go to an abdominal organ or to an extremity; if into a vein, it should go to the right side of the heart. Several possibilities may be considered.

If injected air reaches the venous circulation it will reach the right side of the heart. Then, if there is an interauricular or interventricular septal defect, it will reach the left side of the heart and the systemic arteries, including those of the brain. There is also evidence that air can cross the pulmonary capillary bed and reach the arteries of the systemic circuit.[5]

There are free anastomoses between the pelvic veins and the so-called vertebral venous plexus. The latter is inside the spinal canal. Thus, if air penetrates into some of the pelvic veins in patients receiving artificial pneumoperitoneum, it may pass through the vertebral venous plexus to the intracranial sinuses. Within the cranium, the air may obstruct some of the veins which drain cortical areas.[6]

In venous or pulmonary air embolism, air enters a systemic vein and passes into the right side of the heart. If the quantity of air is sufficient, a typical chain of events follows. First, there is a sensation of bubbling in the left chest, in the region overlying the pulmonary conus. At the same time, the presence of air in the right ventricle produces a churning sound which can often be heard without a stethoscope, and which is known as a mill-wheel murmur.[1] An air-trap forms in the right ventricle, causing obstruction. Obstruction causes elevated venous pressure, cyanosis, and often syncope through cerebral anoxemia. Obstruction also causes forward cardiac failure, with deficient cardiac output and a rapid, feeble pulse. Some air may pass through the right side of the heart into the lungs, where it may cause embolism of small and medium-sized pulmonary arteries. The symptoms are dyspnea, hyperpnea and tachypnea, and these may be so marked that alkalosis and tetany develop.[7, 8]

Venous air embolism may result from surgical operations, from air injections, or from the accidental entrance of air into intravenous apparatus.[9]

Venous air embolism is a rare complication of surgical operations, but it may occur whenever a vein with a negative pressure is cut, leaving open the defect closer to the heart.[10] The pressure in the right auricle is always negative, falling to its lowest level during the height of inspiration. This negative pressure is transmitted to the great veins, approaching zero and eventually becoming positive as the veins become smaller and more distant from the right auricle. The uterine sinuses have been the point of entry of air in a number of cases, in the course of delivery, pelvic operations, vaginal insufflation of air for Trichomonas infestation, and transuterine air injec-

tions.[11] The veins of the neck, chest, and the dural sinuses have been incriminated in a few cases.[10, 12] Some cases have followed upon injections of air into the peritoneal cavity. Faulty technic has resulted in a number of cases during transfusions or intravenous injections.[13, 14]

The prognosis of venous air embolism depends on the amount of air which reaches the circulation, the speed with which it enters, and the position of the body at the time embolism occurs. The treatment consists principally of putting the patient in the left lateral position, which favors the displacement of the air trap and relief of the obstruction. Ventricular puncture and aspiration of air have been reported. Shock should be combated if it exists.

Case 5. This patient was a 57 year old white man who was admitted to the hospital on March 15, 1949. On admission he was febrile; he had a bilateral tuberculous lesion with bilateral cavitation, tuberculous ulceration of the hypopharynx, and a positive sputum. On streptomycin and bed-rest the temperature came down to normal, the ulceration of the hypopharynx healed, and the pulmonary lesion improved; however, the sputum remained positive and the cavities remained open. Physical examination of the abdomen showed the liver edge to be three fingerbreadths below the costal margin.

On October 10, 1949, pneumoperitoneum was attempted. The needle was inserted at a point midway between the umbilicus and the midclavicular line on the left lower costal margin. The plunger of the syringe was drawn back, but no air or blood was aspirated. Two hundred cubic centimeters of air were injected. The patient immediately became cyanotic over the head and neck, respirations became labored, and syncope developed; the pupils became dilated, and death followed in a very short time. It is estimated that less than 10 minutes elapsed between the time the patient was placed on the table and the time he died.

At autopsy the pericardial sac was opened. Then the entire chest cavity was filled with water so that the lungs and heart were entirely submerged. A very small incision was then made into the right ventricle. It was noted that many air bubbles escaped from the right ventricle, along with some bloody froth. The heart was otherwise normal; the coronary arteries were normal and contained no bubbles of air. The liver was found to be enlarged, and there was a small perforation in the left lobe, approximately 1.5 cm. from the edge. No punctured blood vessel was found. The veins of the greater curvature of the stomach were dilated and engorged. The other postmortem findings were irrelevant.

This is a proved case of venous air embolism. The source of the air is known, as well as the mechanism of death. Air was injected into the left lobe of the liver, and found its way directly into the right side of the heart, where it formed an air-trap and effectively obstructed the outflow of blood to the lungs. Blood backed up in the systemic venous circuit, as evidenced by cyanosis of the face and neck and by engorgement of the gastric veins. As little blood reached the lungs, little could return to the left side of the heart, and forward failure resulted. No air passed through the pulmonary capillaries into the coronary arteries, and there is no evidence that air reached any other part of the systemic arterial circulation.

Summary and Conclusions

1. Air embolism exists in two forms, arterial and venous.

2. In arterial air embolism, air enters a pulmonary vein and is ejected from the heart into the systemic arteries of the upper part of the body. This type of embolism occurs as a complication of pneumothorax, pneumoperitoneum, thoracentesis and thoracic surgery. The treatment consists of lowering the head. Death occurs from coronary or cerebral embolism.

3. In venous air embolism, air enters a systemic vein and reaches the right side of the heart. The symptoms are due to obstruction of the circulation by an air trap in the right ventricle. This type of embolism occurs as a complication of surgery involving the larger veins, or of transfusions or intravenous injections. The treatment consists of placing the patient in the left lateral position, which favors the displacement of the air trap and the consequent relief of the circulatory obstruction. Death occurs from circulatory obstruction or obliteration of the pulmonary capillary bed by air.

4. Both types of air embolism are fortunately uncommon. They are so catastrophic, however, that an understanding of their mechanism is important. Most cases can be prevented. When they occur, only immediate recognition and proper treatment will save the patient's life.

BIBLIOGRAPHY

1. Durant, T. M., Long, J., and Oppenheimer, M. J.: Pulmonary (venous) air embolism, Am. Heart J. **33**: 269, 1947.
2. Van Allen, C. M., and Hrdina, L. S.: Air embolism from the pulmonary vein: a clinical and experimental study, Arch. Surg. **19**: 567, 1929.
3. Durant, T. M.: The occurrence of coronary air embolism in artificial pneumothorax, Ann. Int. Med. **8**: 1625, 1935.
4. Pollak, M.: Air embolus, Am. Rev. Tuberc. **28**: 187, 1933.
5. Rangell, L.: Cerebral air embolism, the question of arterialization of intravenous air across the barrier of the pulmonary capillaries: report of a case following assumption of the knee-chest position post partum, with recovery, J. Nerv. and Ment. Dis. **96**: 542, 1942.
6. Banyai, A. L.: Personal communication.
7. Meneely, G. R., and Wells, E. B.: Serious air embolism during blood donation, J. A. M. A. **132**: 141 (Sept. 21) 1946.
8 Megibow, R. S., Katz, L. N., and Feinstein, M.: Kinetics of respiration in experimental pulmonary embolism, Arch. Int. Med. **71**: 536, 1943.
9. Martland, H. S.: Air embolism, with special reference to its surgical importance, Am. J. Surg. **6**: 281, 1945.
10. Hepler, T. K., Truter, J. L., and Hunt, H. J.: Air embolism occurring during mastectomy: report of a fatal case, Am. J. Clin. Path. **17**: 322, 1947.
11. Martland, H. S.: Fatal air embolism due to powder insufflations used in gynecological treatments, Am. J. Surg. **68**: 164, 1945.
12. Hewer, C. L., and Combs, H. I.: Fatal air embolism during mastectomy, Brit. M. J. 1: 97, 1948.
13. Simpson, K.: Air accidents during transfusion, Lancet **1**: 697, 1942.
14. Doyle, G. B., and Frodsham, P.: Fatal air embolism during blood transfusion, Lancet **1**: 735, 1949.

GASTRIC ANTACID AND ANTI-SECRETORY DRUGS: A SURVEY BASED PRIMARILY ON THEIR EFFECTS UPON GASTRIC SECRETION IN MAN *

By Joseph B. Kirsner, M.D., Ph.D., F.A.C.P., Walter L. Palmer, M.D., Ph.D., F.A.C.P., *Chicago, Illinois,* Erwin Levin, M.A., M.D., *Cleveland, Ohio,* and Arthur P. Klotz, M.D., *Chicago*

The medical management of peptic ulcer in large part comprises the use of compounds which either neutralize or inhibit temporarily the output of hydrochloric acid.[1] The rationale of this treatment and evaluation of its therapeutic efficacy are beyond the scope of the present study. The purpose of this paper is rather to survey the current status of antacid and antisecretory drugs with reference primarily to their effects upon gastric secretion in man.

Methods and Criteria for Evaluation of Antacid and Inhibitory Effect

The various procedures for estimating the efficiency of antacid and antisecretory drugs are of limited scope and are further handicapped by the lack of complete knowledge of the mechanism of gastric secretion. In vitro study,[2] though helpful in defining the chemical reactions involved, cannot reproduce the secretory potential of the human stomach and the factors governing its response. Animal experiments, though of interest as a "first approximation," are not directly applicable to man because of species differences in physiologic and pharmacologic response. The normal man is not entirely suitable as a test subject since his output of acid is less than that of patients with duodenal ulcer [3]; neutralization of the normal gastric contents does not necessarily signify a similar result in the hypersecreting stomach. Antacid and antisecretory efficiency, therefore, must be determined directly in the patient with duodenal ulcer, and under well-controlled conditions; indeed, under these circumstances also, the analysis may be complicated by physiologic stimuli, inhibitory as well as stimulatory, which significantly influence the gastric response to drugs.[4] The "spontaneous" fluctuations in the gastric secretion of man are large, and require consideration in the evaluation of results.

Evaluation on the basis of relief of symptoms [5] is handicapped by individual differences in interpretation, inherent in a subjective analysis, and by the inability to exclude the many factors influencing the course of the disease. The beneficial clinical results obtained with distilled water or

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 11, 1951.

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

saline solution [6] are of importance in this connection. Rate of healing of the ulcer crater, as measured roentgenographically,[7] is a useful objective criterion; more information is needed concerning the relation of the size of the crater to the rate of healing; variations in healing time may be pronounced, ranging from one to 20 weeks. Furthermore, the roentgen disappearance of an ulcer crater does not necessarily signify complete healing. The complexity of the therapeutic problem in peptic ulcer is perhaps illustrated further by the observation that complete healing of gastric ulcer may require several weeks or more, despite the total elimination of acid after roentgen irradiation of the stomach.[8] The rate of recurrence, in the final analysis, constitutes the most important measure of any therapeutic program in peptic ulcer; the available information is meager and the studies are not so well controlled as might be desired; Hollander and Mage [9] and Bralow et al.[10] have emphasized some of the difficulties involved in this approach.

The theoretically ideal antacid has been characterized as having (a) palatability; (b) absence of untoward reactions, such as alterations in acid-base equilibrium; (c) prolonged neutralizing effect when administered in small quantities; (d) absence of secondary rise in secretion; and (e) low cost. These qualities, though individually desirable, are not of equal significance, and judgment is necessary to evaluate their relative importance. The development of alkalosis obviously would negate the value of an otherwise efficient antacid. On the other hand, the absence of constipation is of doubtful clinical significance in ulcer therapy when the neutralizing or inhibiting action is negligible. The initial consideration in the evaluation of antacid and antisecretory drugs for clinical application would appear to be their effect upon the gastric contents of man; among those compounds satisfying this primary criterion, the selection obviously would depend upon the presence or absence of undesirable side reactions.

The goal of therapy with antacid and antisecretory drugs presumably is effective neutralization or inhibition of the free acid and peptic activity of the gastric secretion.[11] Antacids influence only the reaction of the gastric contents locally [12]; they do not act upon the parietal cells, hence their effects are limited to the period of administration. Inhibitory drugs, on the other hand, act upon the parietal cells directly or indirectly; their effects, therefore, may be sustained. Berk et al.[13] have demonstrated also that in situ effects of antacids on duodenal acidity in patients with duodenal ulcer cannot necessarily be predicted from their behavior in the stomach. The pH of the gastric contents in patients with duodenal ulcer usually ranges between 1 and 2. Effective neutralization may be defined as maintenance of the pH between 4.0 and 5.5 or higher, since at this hydrogen-ion concentration the free acid and peptic activity are eliminated. Adequate inhibition may be characterized arbitrarily as the complete absence of free acid for periods of perhaps three to six hours or longer. Decreases in acidity and volume may be significant statistically, but in the continued presence of hydrochloric acid

they do not signify adequate control from the viewpoint of effective ulcer therapy.

Antacids

Calcium Carbonate and Other Calcium-Containing Antacids. Calcium carbonate reacts with hydrochloric acid as follows: $CaCO_3 + 2HCl \rightleftarrows CaCl_2 + H_2CO_3 (CO_2 + H_2O)$; the calcium chloride is changed to relatively insoluble calcium phosphate and carbonate in the alkaline intestinal contents.[14] Hourly doses of 2 or 4 gm. usually maintain the pH of the gastric contents at approximately 4.0.[15] The supplementary administration of atropine, 1.0 mg. by mouth four times daily, improves the neutralizing effect, the pH remaining consistently at 5.0. The rôle of atropine apparently is to delay gastric emptying, thus permitting a longer period of interaction between alkali and acid; decreased volume of secretion may be a factor in a few cases. Gastric motility and the retention of an antacid within the stomach are important factors governing the degree of neutralization; rapid emptying into the small intestine will shorten the period of interaction between alkali and hydrochloric acid and decrease the efficiency of neutralization, whereas more prolonged retention of an antacid within the stomach will promote more effective neutralization. Calcium carbonate does not increase significantly the output of chloride in the feces,[16] nor disturb the serum electrolytes. The alkalosis encountered in patients receiving calcium carbonate during the Sippy treatment of peptic ulcer is caused by the loss of chloride in the aspirated or vomited gastric contents and by the insufficient intake of salt; it can be corrected by adequate replacement of salt without discontinuance of calcium carbonate.[17] We have not observed an increased tendency to the formation of renal calculi during the prolonged ingestion of calcium carbonate. The chief disadvantage of this antacid is its constipating action; this can be corrected by the administration of magnesium carbonate.

Tribasic calcium phosphate[18] reacts with hydrochloric acid in the following manner: $Ca_3(PO_4)_2 + 6HCl \rightleftarrows 3CaCl_2 + 2H_3PO_4$; the phosphoric acid limits the rise of pH to perhaps 2.5. The antacid effect is mild and transitory.

Combinations of calcium carbonate with glycine or calcium caseinate[19] have been used clinically, but their antacid efficiency in man has not been reported. The mixture of calcium carbonate, sodium bicarbonate and powdered milk, in quantities of 12.5 gm., neutralizes gastric acidity adequately[2]; however, this preparation has not received much usage, probably because of the tendency of the easily absorbed sodium bicarbonate to produce alkalosis. Davies and Longmuir,[21] on the basis of extensive studies of the mechanism of gastric secretion by isolated frog gastric mucosa, state that the ideal antacid for the prevention of ulceration should evolve CO_2 in the presence of acid, and should contain cations which do not alter the acid-base equilibrium of the blood. The carbonate or bicarbonate of a basic

protein, such as a protamine, and milk saturated with CO_2 are suggested as theoretically good antacids.

Aluminum Hydroxide and Other Aluminum-Containing Antacids. Aluminum hydroxide has achieved wide popularity as an antacid.[22-28] It reacts with hydrochloric acid as follows: $Al(OH)_3 + 3HCl \rightleftarrows AlCl_3 + 3H_2O$; since aluminum chloride is an acid salt, the final pH does not exceed 4.0 and usually ranges between 2.0 and 3.0. The theoretic neutralizing power of aluminum hydroxide, calculated on the basis of dry weight, exceeds that of calcium carbonate. However, large hourly doses of 30 c.c. are required to raise the pH in patients with duodenal ulcer.[15] According to Bralow and his associates,[10] different commercial preparations vary in their neutralizing capacity. A tendency to secondary rise in acidity has been noted,[29] as with practically all antacids. Administered as a continuous intragastric drip, aluminum hydroxide effectively decreases the acidity during the period of administration; the practicality of this type of therapy is limited, however. Aluminum hydroxide also has been characterized as an adsorbent of pepsin,[30] and as an astringent and demulcent. Its capacity to absorb pepsin in vivo seems no greater than that of calcium carbonate [31]; the astringent and demulcent properties do not appear susceptible to scientific measurement in man. Aluminum hydroxide increases phosphate excretion in the feces [16]; however, the ulcer diet contains ample amounts of phosphate, and the acid-base equilibrium of the blood is not disturbed.[32] The constipating effect of this antacid may be pronounced. "Non-reactive" aluminum hydroxide,[33] aluminum phosphate,[34] hydrated sodium aluminum silicate,[35] aluminum dihydroxyaminoacetate [36] and aluminum carbonate [37] do not appear to offer any striking additional advantages.

Magnesium-Containing Antacids. Synthetic hydrated magnesium trisilicate reacts with hydrochloric acid in the following manner: $Mg_2SiO_3 \cdot 2H_2O + 4HCl \leftrightarrows 2MgCl_2 + SiO + 4H_2O$. Its neutralizing and adsorptive properties are described as less prompt but more prolonged than those of other antacids.[38-41] The notion that because an antacid reacts slowly with acid it will neutralize for a long time in vivo is a popular fallacy. Although there is some tendency in this direction, the rate of reaction is not a reliable index of the *duration* of action in vivo. The tendency toward prolonged effect is more directly correlated with the rate of emptying from the stomach. Magnesium trisilicate in quantities of 2 or 4 gm. hourly may partially neutralize the free acid in patients with duodenal ulcer [42]; however, Nicol [43] did not observe a constant or pronounced antacid effect during the hourly administration of one teaspoonful of magnesium trisilicate. (Similar results were obtained with aluminum hydroxide.) Tablets of magnesium trisilicate are less effective. Indeed, our experience indicates that the neutralizing value of any antacid in tablet form is distinctly inferior to that of powdered or liquid preparations because, in this physical state, smaller amounts enter

into the reaction with hydrochloric acid before being emptied into the intestine.

Magnesium oxide reacts as follows: $MgO + 2HCl \rightleftarrows MgCl_2 + H_2O$. Its neutralizing capacity in vitro surpasses that of all other alkalis. Because of its laxative effect, magnesium oxide is prescribed only to regulate bowel activity. Magnesium carbonate,[42] in hourly doses of 2.0 gm., neutralizes gastric acidity satisfactorily; it also is of value primarily as an anticonstipating agent. Tribasic magnesium phosphate [42] has a mild, transient antacid effect, resembling tribasic calcium phosphate. The chemical reactions are similar: $Mg_3(PO_4)_2 + 6HCl \rightleftarrows 3MgCl_2 + 2H_3PO_4$. Adequate neutralization has been reported with a mixture of tribasic magnesium phosphate (25 per cent), tribasic calcium phosphate (50 per cent) and silica (25 per cent).[44] Combinations of magnesium trisilicate and aluminum hydroxide,[45] magnesium hydroxide alone [46] and together with aluminum hydroxide [47] or with a urea-formaldehyde combination [48] have been recommended; their effects upon the gastric content of man have not been studied sufficiently.

Other Antacids. Favorable clinical results recently have been reported [10, 49] with sodium carboxymethylcellulose (SCMC) administered as a 5 per cent solution, or as tablets containing 450 mg. of SCMC and 150 mg. of magnesium oxide. Sodium carboxymethylcellulose is described as a salt of a polycarboxylic acid, similar to the polyglucuronic acid component of normal gastric mucus.[50] It exchanges sodium ions for hydrogen ions and acts as a true buffer because it is a salt of a weak organic acid (carboxymethylcellulose) and a strong base (sodium hydroxide). The carboxymethylcellulose formed in the stomach is reconverted to the neutral sodium salt by the alkaline duodenal secretions. The preparation is stated to protect against histamine-induced ulcers in the dog and to form rapidly a protective, tenacious demulcent coating over the gastric mucosa and ulcer. The absence of constipation is regarded as a further advantage. In a series of 105 patients with peptic ulcer treated with SCMC (containing 450 mg. sodium carboxymethylcellulose and 150 mg. magnesium oxide), 61 per cent were completely asymptomatic at the end of one year, as compared with 40 per cent of 100 patients receiving aluminum hydroxide. The recurrence rates for the two groups were 23.8 and 34 per cent, respectively. These differences are not impressive. Carefully controlled studies of gastric secretion in man and additional clinical studies are necessary before this compound can be fully evaluated.

Mucin prepared from the hog's stomach possesses low neutralizing power in man [51]; this is due to the peptones in the preparation and not to the mucin per se; its value in ulcer therapy is considered to be that of protecting and lubricating the mucosa.[52] Of interest in this connection is the presence of an inhibitory agent for gastric secretion in the dog, isolated from fresh gastric and salivary mucin by Code et al.[53] The mixture of purified gastric mucin, magnesium trisilicate and aluminum hydroxide temporarily decreases

but does not completely neutralize the free acid in man [54, 55]; the coating effect ascribed to this preparation and to other substances requires confirmation; if it exists, its therapeutic value remains to be established. Bismuth salts have no antacid effect. Zirconium phosphate [56] is less efficient than aluminum hydroxide. Sodium citrate and sodium acetate have been suggested as antacids but their value seems doubtful, since the easily absorbed sodium ion might result in alkalosis.

Intragastric Drip. A regimen of milk and cream and antacids hourly during the day and early evening, and atropine sulfate periodically, may neutralize the gastric contents effectively during the period of treatment, but it does not control the excessive nocturnal gastric secretion characteristic of patients with duodenal ulcer. The recent observations of Breuhaus et al.[57] coincide with our findings that daytime treatment exerts little effect on the nocturnal secretion. Continuous effective neutralization may be accomplished by the intragastric drip, a procedure introduced by Winkelstein [58] and later adopted by others.[59] Three liters of milk containing either aluminum hydroxide (diluted with three volumes of water) or aluminum phosphate are administered through a nasogastric tube during a 24-hour period, at a rate of 125 c.c. per hour. Clark [59b] prefers fresh milk citrated with 2.4 gm. of sodium citrate to the pint; however, the easily absorbed sodium ion may cause alkalosis. The pH of the gastric contents usually is maintained between 3.5 and 4.0.[60] The intragastric drip may be continued for 10 to 14 days, occasionally for three weeks. It is especially helpful to patients with hypersecretion and severe ulcer distress, and in some instances of massive hemorrhage. The drip treatment is not practical for general or prolonged use; it is contraindicated in the presence of pyloric obstruction.

Protein Hydrolysates. In vitro studies [61] suggest that protein hydrolysates in large amounts possess sufficient neutralizing power to increase the pH of the gastric content to 3.5. Levy [62] found a 10 per cent solution more effective in buffering histamine-stimulated secretion in man than either milk or a 10 per cent solution of pure casein in water. The mixture of hydrolysate in milk surpassed either alone. Differing results have been reported by other investigators.[63–66] A 10 per cent solution of hydrolysate given hourly (25 gm.), or as a continuous intragastric drip, did not neutralize the free acidity adequately, in the experience of Woldman et al.[63] Pronounced secondary increases in secretion are frequently observed after a brief period of neutralization, whether the dose is small (9 gm.) or large (50 gm.).[64, 65] A mixture of 30 gm. of casein hydrolysate and 30 gm. dextrimaltose No. 2 neutralized gastric and duodenal bulb acidity over a two-hour period better than did milk or a 5:1 mixture of milk and cream.[67] The antacid effect was imperfect, however, and the acidity subsequently exceeded control values. The varying results may be related to differences in gastric emptying, for Sun and Machella [68] observed more effective reduction of gastric acidity upon the addition of atropine to a hydrolysate regimen.

The intravenous infusion of protein hydrolysates almost invariably increases gastric secretion in man.[69, 70] Present evidence indicates that, while protein hydrolysates are of nutritive value, their neutralizing efficiency is distinctly inferior to that of ordinary antacids. The unpalatability of some hydrolysate mixtures would appear to be a further disadvantage.

Resins. Anion exchange resins are large insoluble bases with the capacity to absorb the anion of an acid, forming an insoluble resin salt[71, 72]; in the alkaline intestinal contents, the anion exchange is reversed and the resin is restored to its original form. Amberlite IR–4 (particle size 200 mesh), a polyethylene polyamine substituted resin of diphenylol dimethyl methane and formaldehyde in basic form, is reported to have yielded satisfactory clinical results in peptic ulcer.[73–75] Quantities up to 28 gm. by mouth daily do not cause significant untoward effects. The resin is capable of partially neutralizing hydrochloric acid and decreasing peptic activity in vitro.[76, 77] Secretory studies in man have been made only occasionally. Doses of 0.25 gm. very temporarily decreased the free acid (Ewald meal) in patients with peptic ulcer; transient increases were observed in some cases 15 minutes later. Very large quantities are required to neutralize the acidity for one hour.[78] Amberlite IR–4, in doses of 3.2 gm. in 50 c.c. of water, diminished the acidity and peptic activity in both stimulated (histamine, insulin) and unstimulated gastric secretion among ulcer and nonulcer patients.[79] Comparable results were obtained with the small dose of 0.6 gm. of a mixture of calcium carbonate, sodium bicarbonate and bismuth subcarbonate, and with 0.6 gm. of aluminum hydroxide. The neutralizing effect of all three preparations cannot be regarded as impressive, however. More effective antacids are available than the combination selected for control purposes in this study. The combination of polyamine methylene resin with gastric mucin is reported to have yielded encouraging clinical results; although antacid effect upon basal-histamine gastric secretion was observed, the reduction in free HCl was not pronounced.[80] The time required for the roentgen disappearance of duodenal ulcer craters was reported as significantly shortened in patients given amberlite IR–100 in comparison with individuals receiving aluminum hydroxide; the effect of the resin upon gastric secretion was not determined.[81] Anion exchange resins may partially reduce gastric acidity in man; they do not appear to be superior to other antacids, and are less effective than calcium carbonate.

Detergents. Sodium alkyl sulfate, a synthetic detergent of the anionic series, eliminates the peptic activity of gastric juice in vitro, the decyl and dodecyl derivatives being most active.[82, 83] This effect, in contrast to the action of calcium carbonate or aluminum hydroxide, is accomplished without significant change in pH from the acid range. Synergistic effects have been described with combinations of sodium alkyl sulfate and aluminum hydroxide[84] or with a polyamine resin.[85] Other anionic detergents also diminish peptic activity in vitro to a varying degree. Inhibition of peptic activity,

reduction in secretion and prolonged survival from histamine-induced ulcers have been reported in the dog.[86, 87] However, large amounts of sodium alkyl sulfate do not decrease the peptic activity of the gastric contents in man,[88, 89] probably because of the blocking effect of certain lipids.[88] Only slight and transient decreases in peptic activity occur in patients with peptic ulcer given both the detergent and a low-fat diet; the course of gastric ulcer is unaffected.[90, 91] The experience with sodium alkyl sulfate once again demonstrates that results in the test tube or the dog are not automatically transferable to man.

Inhibition of Gastric Secretion

Antacid therapy, to maintain its effectiveness, must be continued for long periods of time. The mode of administration of antacids is important. The occasional intake of an alkali, perhaps three or four times daily, a common practice, is inadequate antacid therapy and reflects lack of knowledge of the secretory capacity of the human stomach and of the action of the antacid. The administration of an alkali solely after each meal is inefficient; food itself possesses some buffering capacity and antacid effect (pH rise to 3.0); hence the concomitant intake of an antacid would seem to be unnecessary at this time. Effective antacid treatment comprises the almost continuous administration of an antacid, milk and cream and soft bland foods, as originally described in the Sippy regimen, or in the form of a drip. This program most effectively neutralizes gastric acidity. However, the hourly intake of medication is not practical for prolonged use; many patients eventually find the régime tedious and distasteful and, consequently, are reluctant to continue it indefinitely. Furthermore, it must be admitted that, although such a program efficiently relieves ulcer pain and provides the conditions for the healing of a given ulcer, recurrences of peptic ulcer continue to be a major problem. A more attractive and probably more practical form of treatment would be the effective inhibition of gastric secretion by parenterally or, preferably, orally administered drugs. The elimination of free acid, irrespective of other factors possibly implicated in the pathogenesis of peptic ulcer, would eliminate the ulcer problem. This exciting possibility is receiving much attention at present.

Antihistamines. Attempts to inhibit the secretion of hydrochloric acid by counteracting the effects of endogenously produced histamine have been generally unsuccessful. Histaminase prepared from fresh hog's kidney, in earlier experiments, did not depress gastric secretion either in the dog or in man [92–95]; inhibition of the response to histamine recently has been reported in dogs following the intravenous injection of an apparently more potent and less toxic material prepared from the hog renal cortex.[96] Benadryl (β-dimethyl amino ethylbenzhydryl ether hydrochloride), pyribenzamine (N^1-pyridyl-N^1-benzyl-N-dimethyl-ethylene diamine hydrochloride), and similar compounds (antistin, anthisan) may antagonize the action of histamine upon

the gut of animals, but their effect upon gastric secretion is negligible.[97-99] Temporary decreases in the secretory response to alcohol or histamine have been reported,[100, 101] but other studies in man have yielded completely negative results.[102-105] Antihistamines may, indeed, stimulate gastric secretion.[106-108] In our laboratory, the nocturnal gastric secretion in patients with peptic ulcer was unaffected by combinations of benadryl (50 mg.) and atropine (1.0 mg.), administered parenterally in three doses within 12 hours, or by the combination of benadryl, atropine and ephedrine. Antihistamine therapy may be complicated by agranulocytosis.[109] These compounds are of no value in the management of peptic ulcer.

Enterogastrone; Urogastrone. Enterogastrone is the hormone (chalone) elaborated by the mucosa of the upper small intestine, responsible physiologically for the decrease in gastric secretion and motility which occurs when adequate concentrations of fat or sugar are present in the lumen of the upper intestine.[110] Concentrates of enterogastrone, prepared from the intestinal mucosa of hogs and given intravenously, diminish the secretory response of dogs with Pavlov pouches to various stimuli, and they eliminate the abnormal secretory response of dogs subjected to the Mann-Williamson operation.[110, 111] Both positive and negative results have been observed in the cat.[112] In patients with duodenal ulcer, the nocturnal and 24-hour gastric secretion may decrease after the intramuscular injection of 1,000 to 3,000 mg. of an enterogastrone concentrate.[113] The inhibition is variable in degree, temporary in duration and not directly correlated with the dosage. The secretory response to histamine or insulin was unchanged in a small series of patients.[114] More consistent but temporary decreases in the nocturnal gastric secretion have been observed after the intramuscular injection of 5,000 mg. of a dialyzed preparation.[115] The inhibitory effect consists chiefly of a reduction in the concentration of acid; the volume may be unaffected or lowered in varying degree. Large amounts of enterogastrone by mouth for long periods of time have little or no effect upon gastric secretion in man.[116, 117] Thus, the possible protective action of enterogastrone against recurrence of peptic ulcer in man [118] is not related to an antisecretory influence.

Beneficial clinical results with extracts of gastric and duodenal mucosa from the hog (Robuden) and with deproteinized extracts of the mucosa of the stomach and of the small intestine from recently killed animals have been reported by European investigators [119]; however, in a well-controlled study the results obtained with placebo treatment were similar to those obtained with the extracts. The effect of these substances upon gastric secretion seems not to have been studied in man.

Urogastrone refers to a nonpyrogenic extract from the urine of males and nonpregnant females which is apparently capable of depressing gastric secretion in man and in animals when given subcutaneously; oral administration is without effect [110b, 120]; reduction of the volume of gastric secretion

and lowered acidity have been noted in ulcer patients, but the results are inconsistent. Urogastrone apparently is not identified with enterogastrone or sex hormones; its clinical status remains uncertain. When suitable preparations are available, it will be of interest to investigate the effect of intravenously-administered enterogastrone and urogastrone, because this is the only highly effective route experimentally.

Sex Hormones. A relationship between gastric secretion, peptic ulcer and endocrine activity has been suggested by numerous writers, chiefly because of the higher incidence of peptic ulcer in males and the apparent infrequency of active ulcer during pregnancy.[121, 122] In addition, a decrease in gastric acidity early in pregnancy [123] has been correlated with an increase in the urinary excretion of chorionic gonadotropins.[124] Experimentally, chorionic gonadotropins intravenously have diminished the output of acid in dogs with Pavlov pouches.[125] A decrease in the incidence of Mann-Williamson ulcers also has been reported [126]; however, it was shown subsequently that extracts of urine free of chorionic gonadotropins were equally effective. Gastric secretion in man has not been inhibited by estrogens,[122, 127-130] antuitrin-S (chorionic gonadotropin),[121] progesterone, or by an extract of pregnant mares' urine ("uro-enterone").[131] Beneficial therapeutic effects recently have been claimed for this latter substance in "intractable" duodenal ulcer; more evidence is needed to substantiate these claims. The administration of 20,000 I.U. of a chorionic gonadotropin preparation to a male patient with duodenal ulcer reduced the output of acid by 40 per cent; 7,500 to 20,000 I.U. very markedly diminished insulin-stimulated gastric secretion.[132] The presence or absence of toxic reactions is not clearly stated. It should be reëmphasized, perhaps, that in studying the antisecretory effect of various compounds the objective should be effective reduction of gastric acidity without toxic reactions; such reactions in themselves and regardless of the compound will tend to diminish the output of acid. We have studied this problem recently in more than 100 patients with duodenal ulcer (chiefly males).* [133] Estrogens, progesterone, gonadotropins from the serum of pregnant mares and testosterone propionate, administered intramuscularly in large amounts, did not depress the nocturnal and diurnal gastric secretion significantly. Decreases in the volume and acid output, 50 per cent or more of the control values, were observed occasionally after the injection of chorionic gonadotropin from human pregnancy urine alone and together with estrogens. Similar results were obtained in studies of the one-hour basal secretion and one-hour histamine response, measured before and again five days after the daily administration of these hormones in large quantities. Other hormones, such as desoxycorticosterone acetate, reportedly effective clinically,[121d] and parathyroid extract in large doses do not inhibit basal or histamine-stimulated gastric secretion in patients with duodenal ulcer. The

* This investigation has been supported by a grant-in-aid from The National Institutes of Health, U. S. Public Health Service.

negative results with parathyroid extract are in contrast to previous reports in dogs [134] and in man.[135] Evidence has been presented indicating that ACTH stimulates gastric gland activity by way of the adrenal gland to produce an increase in gastric juice as well as in urinary uropepsin.[136] Our observations are in agreement. It is of interest in this connection that the levels of histamine in the blood may rise during ACTH therapy. Clinical reports are now emphasizing the occurrence of hemorrhage and perforation during ACTH therapy both in patients with known peptic ulcer and in individuals not previously suspected of having peptic ulcer.[137] The use of ACTH in known ulcer cases, therefore, is unwise.

Cholinergic Blocking Agents

The chemical development of gastric antisecretory agents may be divided into several phases: the synthesis of simplified analogs of atropine, incorporating various groupings of that molecule into amino alcohol esters, such as trasentine and pavatrine; the preparation of simple quaternary ammonium salts, such as tetraethylammonium and hexamethonium compounds; and the combination of the amino alcohol ester structure with the quaternary ammonium structure of TEA, resulting in such compounds as banthine (Searle), and U–0407 (Upjohn) and others; these substances seem to have sufficient selective parasympatholytic action, decreasing gastric secretion and gastrointestinal motility, without producing too much of atropine's central stimulating and mydriatic effects or TEA's hypotensive properties. Other groups of cholinergic blocking agents have been developed, but at present there is little information concerning their clinical effects.[138]

Atropine. The action of atropine apparently is peripheral, preventing the response of the vagal neurocellular junctions to the acetylcholine liberated at the postganglionic parasympathetic nerve endings. It effectively decreases gastric secretion in the dog.[139] The results in man have differed widely, possibly because of fluctuations in dosage and method of study.[140] Apparently in the normal man atropine may abolish temporarily all phases of gastric secretion and suppress partially the response to histamine or alcohol. The effects are less pronounced in the patient with duodenal ulcer. Inhibition of gastric secretion usually is accompanied by toxic symptoms; these include blurring of vision, dryness of the mouth and tachycardia; mental confusion and visual and auditory hallucinations develop occasionally. The effect of atropine upon gastric secretion in man recently has been reinvestigated in our laboratory; 172 studies were made in 35 patients.[141] The results were variable and unpredictable; toxic symptoms developed in all patients manifesting significant inhibition of secretion. A depression of acid secretion (exceeding 25 per cent of control values) occurred in approximately one-third of the studies. Doses of 2.0 mg. appeared to be no more effective than 1.0 mg.; repeated injections of 2.0 mg. every four hours (three doses) were not more effective than 1.0 mg. The incidence of posi-

tive and negative results did not appear to correlate with the rate of secretion. Similar data have been published by Mears.[142] We found that the intramuscular administration of atropine (1.0 mg.) and adrenalin [143] in oil (2 mg.) reduced the concentration of acid more frequently than atropine alone.

The synthetic atropine-like compounds, syntropan, trasentine, bentyl hydrochloride and similar substances,[140, 144] are less effective than atropine. Syntropan (amprotropine hydrochloride), in doses of 10 to 25 mg. intravenously, 10 to 50 mg. subcutaneously, and 100 to 200 mg. by intestinal infusion, does not reduce significantly the volume or acidity of the gastric contents.[146] Trasentine (adiphenine hydrochloride), according to Clark,[147] has relatively slight inhibitory effect on gastric secretion, even in the dog.

Quaternary Amines. Tetraethyl ammonium chloride (TEAC) and bromide (TEAB) are quaternary ammonium compounds, similar structurally to acetylcholine. They have the capacity to block at the autonomic ganglia the transmission of both sympathetic and parasympathetic nerve impulses, this effect probably being attributable to the replacement of acetylcholine at the autonomic synapse, thus excluding it. TEAC and TEAB, in doses approximating 20 mg./kg. of body weight every four to six hours, inhibit gastric secretion and motility in man.[148-153] Significant decreases have been noted in the nocturnal gastric secretion [153] and in the secretory response to alcohol, histamine and insulin in patients with peptic ulcer.[154] This effect is temporary, however; the drug is not effective when given orally. Side effects include local tenderness and burning, numbness, tingling, weakness, faintness, blurring of vision, dryness of the mouth, rise in pulse rate, and postural hypotension. Toxic effects following the administration of TEAB are reported in animals and man.[155] Among 20 dogs given large doses seven died, five from curariform paralysis of the intestinal and diaphragmatic muscles, and two probably from central respiratory paralysis. A similar nonfatal paralysis was observed in man. TEAC and TEAB are of limited value in the treatment of peptic ulcer because of the relatively brief duration of effect and the side reactions, and because these drugs can be administered only in hospitalized patients. The use of tetraethylammonium compounds is contraindicated in severe hypertension and renal disease and probably in massive hemorrhage.

Hexamethonium iodide, a member of the homologous series of polymethylene-bistrimethyl-ammonium compounds, also exerts a profound effect on gastric secretion and motility [156]; in therapeutic doses it apparently has no curare-like action and no marked effect on the blood pressure. A quantity of 100 mg. intravenously reduced gastric acidity to zero for three to four hours in patients with duodenal ulcer secreting considerable amounts of acid. Hexamethonium depressed the secretory response to insulin but not that provoked by histamine. Three injections of 100 mg. of hexamethonium, at 8 p.m., midnight and 4 a.m., reduced the volume of the night secretion

to less than half and also greatly lowered the acidity. Quantities of 100 mg. intramuscularly delay gastric emptying and diminish gastric and small intestinal motility. According to Kay and Smith,[156] hexamethonium iodide appears to have several advantages over other drugs with similar pharmacologic action: it can be administered orally, and it has more uniform effect, greater potency and less frequent undesirable side reactions. Hexamethonium iodide in doses of 500 mg. by stomach tube may depress temporarily gastric secretion in patients with duodenal ulcer. Side effects consisted of postural hypotension and, less frequently, blurring of vision, dryness of the mouth and tendency to constipation. Scott et al.[157] report encouraging clinical results in the treatment of duodenal ulcer with hexamethonium bromide, in doses of 500 mg. by mouth three times daily. There was no evidence of cumulative inhibitory effect upon gastric secretion in response to continued treatment. The postural hypotension and syncope produced by hexamethonium compounds may render the drug unsuitable for ambulant patients.

Banthine (β-diethylaminoethyl xanthene-9-carboxylate methobromide), another quaternary ammonium compound, is receiving extensive clinical trial. Animal experiments indicate that banthine incorporates the pharmacologic actions of both atropine and the tetraethylammonium compounds.[158] Longino et al.[159] noted a consistent decrease in the volume of gastric secretion and in the free and total acidity in patients with duodenal ulcer given banthine intravenously (0.2 mg./kg. body weight) or orally (100 mg.). Smith et al.[160] similarly reported a reduction in the volume of secretion and output of acid in the nocturnal gastric secretion of patients with duodenal ulcer given 100 mg. of banthine by mouth; the interpretation is open to some question in view of the "spontaneous" fluctuation in acidity and the small number of cases. Dosages of 25 to 50 mg. orally one hour before insulin-induced hypoglycemia did not block the subsequent gastric secretory response. In a series of patients with duodenal ulcer studied in our laboratory, the intramuscular injection of small amounts of banthine (as low as 0.03 mg./kg. body weight) significantly decreased the fasting secretion for from one to four hours in the majority of subjects.[161] The secretory response to insulin hypoglycemia was not modified by two injections each of 25 mg., one-half hour preceding and following the administration of insulin. The response to histamine was unaltered in more than 20 patients, after one to six months of treatment with 200 to 300 mg. of banthine by mouth daily. Banthine partially inhibits the secretory response to histamine in dogs with vagotomized pouches of the entire stomach, and depresses both basal and histamine-stimulated secretion in man.[162] Walters et al.,[163] in a study of 10 patients, eight with duodenal ulcer, found that 100 mg. of banthine by mouth in 30 c.c. of water decreased the volume of gastric secretion without significantly altering gastric acidity. The intravenous administration of 25 to 30 mg. of banthine induced cessation of gastric peri-

stalsis within 30 seconds; preëxisting mucosal hyperemia appeared to blanch moderately.[164] To date, serial measurements of the pH of the gastric content in more than 20 patients with duodenal ulcer in our laboratory have not demonstrated effective inhibition of gastric acidity with 50 to 100 mg. of banthine by mouth; decreases in acidity have been observed occasionally in normal individuals. Encouraging clinical results with banthine have been reported by Grimson and his associates [165] and others.[166] Therapy consists initially in the administration of 100 mg. orally every six hours (400 mg. daily); after two to eight weeks, the dose is reduced to 50 mg. every six hours and is maintained at this level indefinitely (200 mg. daily). Some clinicians prefer a smaller dosage schedule. Winkelstein [167] advocates the use of 50 mg. before meals, another dose on retiring and one during the night. Since the inhibitory effect of 100 mg. of banthine upon gastric secretion was inconsistent, the concomitant use of alkalis is recommended. Occasional patients with severe nocturnal ulcer pain were not relieved by banthine but responded to continuous antacid administration by the drip technic. Banthine causes dryness of the mucous membranes, dilatation of the pupils and loss of visual accommodation; urinary retention may develop in male patients with prostatic hypertrophy; these manifestations may subside without change in treatment, or may necessitate either reduction in dosage or discontinuance of the drug. Banthine increases the cardiac rate; hence it should be administered with caution or avoided entirely in patients with coronary insufficiency and other cardiac disorders. Other side effects may include drowsiness, headache and constipation. The drug is contraindicated in existent or incipient glaucoma and in prostatic hypertrophy. The drug has not proved helpful in patients with cicatricial duodenal stenosis. We have observed recurrences of peptic ulcer in several patients during therapy with banthine.

Lorber [168] found that dibuline (dibutyl methane of dimethyl-ethyl-β-hydroxyethyl ammonium sulfate) markedly diminished the volume of the interdigestive secretion; atropine was equally effective over a longer period of time, but produced more toxic effects. Dibuline in doses of 40 mg. partially suppressed the response to histamine and insulin; given every four hours, the drug greatly diminished the volume of the nocturnal gastric secretion in patients with uncomplicated duodenal ulcer. We studied the effect of dibuline in 15 patients.[169] Dosages of 10 mg. intramuscularly every four hours during the night yielded results similar to those obtained with atropine; the depressant effect, whenever it occurred, was variable and brief.

Newer Cholinergic Blocking Agents. Several new compounds have been made available recently for clinical investigation.[170] We have studied the antisecretory effect of U–0407 * (Pyrrolidyl ethyl phenyl cyclopentenyl acetate ethobromide) thus far in 26 patients. The procedure employed in

* Kindly provided by the Upjohn Company.

our laboratory for this type of investigation consists of continuous aspiration in fasting patients known to secrete acid continuously; collections of gastric content are made at 15 minute intervals. After a control period of 90 minutes, a quantity of the compound is injected intramuscularly; aspiration is maintained until acid secretion returns to control levels in those subjects in whom the output of acid is suppressed, and for several hours when acid secretion is unaffected. Significant inhibition of gastric secretion consists of the complete absence of hydrochloric acid and the total or nearly complete absence of gastric content. The minimal effective dose of U–0407, 0.04 mg. per kg. body weight, may depress acid secretion for 45 to 90 minutes. Single doses of 0.05 mg. per kg. body weight, or more, inhibit the output of acid for three hours. At minimal effective doses the side effects observed with U–0407, especially dryness of the mouth, appear to be less pronounced than with banthine.

We have investigated the antisecretory effect of Prantal * (N,N dimethyl 4-pyridylidene 1,1-diphenyl methane methylsulfate) in 22 patients. In doses of 0.25 mg. per kg. body weight, inhibition of gastric secretion may continue for from one to one and one-half hours. The response to this drug seems more variable than to the preceding two compounds. Thus total doses of 75 mg. proved ineffective in some instances, whereas in others this dosage of Prantal suppressed the output of acid for from two and one-half to five hours. In four patients, single doses of 50 to 150 mg. by mouth failed to inhibit gastric secretion significantly. Side effects have been minimal, consisting of slight dryness of the mouth.

Numerous additional cholinergic blocking agents related to the foregoing compounds or synthesized as a consequence of them are in the process of preparation. This approach to the treatment of peptic ulcer is receiving intensive study at the present time; it seems to be the most promising development in many years in the search for efficient gastric antisecretory agents.

Miscellaneous Drugs. The effect of sedatives upon gastric secretion has been studied only occasionally. Transient inhibition of acid output has been reported in dogs given large amounts of barbiturates.[171] Noble [172] found that the commonly-used barbiturates were without effect in the cat until near-anesthetic doses were administered. In man, phenobarbital (120 to 180 mg.) and sodium phenobarbital (60 to 180 mg.) did not inhibit gastric secretion significantly.[173] We administered large amounts of sodium amytal intramuscularly (three doses, each of 0.2 gm., at hourly intervals) to 15 patients (12 with duodenal ulcer).[174] Appreciable decreases were observed in the volume of secretion in seven; for the entire series, the output of acid diminished significantly though temporarily in 11 ulcer patients.

The intranasal insufflation of a powdered extract of the posterior pituitary gland (40 mg. four times daily, after meals and at bedtime) is re-

* Kindly provided by the Schering Corporation.

ported to have produced satisfactory clinical results in ulcer therapy.[175] The rationale of this type of therapy is not clear. Extracts of posterior pituitary may decrease gastric secretion in dogs and in man for brief periods, presumably on the basis of vasoconstriction, but the data are insufficient to permit adequate evaluation of inhibitory effect.

Other substances inhibit gastric secretion experimentally; these include urea [176] (satisfactory clinical results have been reported with 15 gm. five times daily by mouth) and a secretory depressant in the gastric juice of patients with pernicious anemia or gastric carcinoma.[177] Quinine bisulfate or atabrine intravenously markedly decreases the vagal-stimulated gastric secretion in dogs.[178] British investigators, on the basis of these observations, have studied the antisecretory effect of the antimalarial compound, paludrine, in man.[179] Quantities of 0.9 to 1.0 gm. by mouth apparently depress moderately and temporarily the response to a gruel meal; paludrine intravenously does not inhibit the response to histamine.

Comment

The present survey indicates that none of the available antacids completely neutralizes the free acidity in man for prolonged periods. Relatively large quantities, 10 to 20 times in excess of that necessary for in vitro experiments, are required to lower the free acidity in man for brief periods of time, probably because of gastric emptying and the continued secretion of acid. "Rebound" increases in acidity have been reported with all antacids; these are difficult to measure accurately, but they undoubtedly occur in varying degree and further impair the efficiency of antacid therapy. Calcium carbonate appears to be the most effective of the many antacids in current use. In hourly doses of 2 or 4 gm., together with milk and cream and atropine, 1.0 mg. two to four times daily, calcium carbonate usually maintains the pH of the gastric contents between 4.0 and 5.5 in patients with duodenal ulcer; it does not cause alkalosis, as has been assumed, and its constipating effect can be corrected with proper substitution of laxative antacids. This regimen, however, is effective only during the period of administration; it does not control the excessive nocturnal gastric secretion of duodenal ulcer. The continuous intragastric drip is perhaps more effective for this purpose, but its applicability is limited. Aluminum hydroxide, magnesium trisilicate or tribasic calcium phosphate in large quantities diminish but do not completely eliminate the free acidity; their neutralizing effect is much less or nil when administered at long intervals and in small amounts, as is the custom of some clinicians. A large number of antacid combinations is available; the evidence for their alleged individual superiority does not seem conclusive. The antacid efficiency of sodium carboxymethylcellulose in man remains to be determined. Protein hydrolysates are less effective than calcium carbonate even when administered in large amounts, and they provoke a secondary rise in secretion exceeding

original levels. The neutralizing capacity of available resins in vivo is not impressive. Detergents such as sodium alkyl sulfate do not alter the pH of the gastric contents, and their antipeptic action in man is insignificant. Mucin has little neutralizing value.

Antihistamines do not depress gastric secretion in man. The antisecretory effect of presently available enterogastrone concentrates is variable and unpredictable. With the possible exception of chorionic gonadotropin and the combination of chorionic gonadotropin and estrogen, the inhibitory effect of various sex hormones, injected intramuscularly in large amounts, appears minimal. Other hormones, such as parathyroid extract, desoxycorticosterone acetate and ACTH, likewise do not inhibit gastric secretion in vivo. Nevertheless, further investigation of hormonal factors regulating gastric acidity seems desirable.

Atropine produces extremely variable effects in patients with duodenal ulcer; in doses effectively inhibiting gastric secretion, it causes toxic symptoms; its principal usefulness may be to enhance the degree of antacid neutralization by prolonging gastric emptying. Synthetic atropine-like compounds offer no particular advantage, and their inhibitory effect in patients with duodenal ulcer is not impressive. In contrast to the preceding compounds, the results obtained thus far with other cholinergic blocking agents are promising. Tetraethylammonium salts significantly depress gastric secretion and motility in man; however, this action is brief and is accompanied by undesirable side reactions. Hexamethonium compounds have yielded promising preliminary results. Banthine parenterally apparently induces a more pronounced inhibition of gastric secretion with fewer toxic manifestations. Clinical results to date are encouraging, although we have noted recurrent ulcers during banthine therapy. A longer period of observation obviously is necessary for complete evaluation of this drug and similar compounds. Newer cholinergic blocking agents are becoming available for clinical trial. There is no evidence at present to indicate that these agents induce the physiologic effects to be expected from complete vagotomy. Nevertheless, they represent a promising advance in ulcer therapy and permit in many cases a more liberal regimen of antacids and diet. The continued exploration of hormonal factors, of drugs acting upon enzyme systems possibly implicated in the mechanism of gastric secretion, and the further development of cholinergic blocking agents may yet lead to the synthesis of a highly effective and safely administered compound for the sustained elimination of free acid in the stomach of man. This accomplishment will provide the solution to the problem of peptic ulcer.

BIBLIOGRAPHY

1. (a) Kirsner, J. B., and Palmer, W. L.: The present management of peptic ulcer, Illinois M. J. **94**: 357, 1948.
(b) Jones, C. M.: Medical and surgical treatment of peptic ulcer, Bull. New York Acad. Med. **25**: 488, 1949.

2. (a) Johnson, E. H., and Duncan, J.: The chemical testing of antacids, Quart. J. and Year Book Pharmacy **18**: 251, 1945.
(b) Holbert, J. M., Noble, N., and Grote, I. W.: A study of antacid buffers. I. The time factor in neutralization of gastric acidity, J. Am. Pharm. A. **36**: 149, 1947. II. Prolonged neutralizations, *Ibid.* **37**: 292, 1948.
3. Levin, E., Kirsner, J. B., Palmer, W. L., and Butler, C.: Nocturnal gastric secretion: studies on normal subjects and on patients with duodenal ulcer, gastric ulcer and gastric carcinoma, Arch. Surg. **56**: 345, 1948.
4. Wolf, S.: Effects of suggestion and conditioning on the action of chemical agents in human subjects—The pharmacology of placebos, J. Clin. Investigation **29**: 100, 1950.
5. Batterman, R. C., and Ehrenfeld, I.: The ambulant treatment of the peptic ulcer syndrome: The comparative effectiveness and constipating action of antacids, Gastroenterology **9**: 141, 1947.
6. (a) Sandweiss, D. J.: Treatment of gastroduodenal ulcer with histidine monochloride (larostidin), J. A. M. A. **106**: 1452, 1936.
(b) Flood, C. A., and Mullins, C. R.: Treatment of peptic ulcer by means of injections, Am. J. Digest. Dis. **3**: 303, 1936–37.
7. (a) Cummins, G. M., Jr., Grossman, M. I., and Ivy, A. C.: A study of the time of "healing" of peptic ulcer in a series of sixty-nine cases of duodenal and gastric craters, Gastroenterology **7**: 1, 1946.
(b) Pollard, H. M., Bachrach, W. H., and Block, M.: The rate of healing of gastric ulcers, Gastroenterology **8**: 435, 1947.
8. Ricketts, W. E., Palmer, W. L., Kirsner, J. B., and Hamann, A.: Radiation therapy in peptic ulcer, Gastroenterology **11**: 789, 807, 1948.
9. Hollander, F., and Mage, S.: A statistical method for evaluating the results of treatment for peptic ulcer, Surg., Gynec. and Obst. **76**: 533, 1943.
10. Bralow, S. P., Spellberg, M. A., Kroll, H., and Necheles, H.: Peptic ulcer in man. I. The ulcer problem. II. The status of ulcer therapy. III. Evaluation of ulcer therapy, Am. J. Digest. Dis. **17**: 41, 86, 119, 1950.
11. (a) Hollander, F.: What constitutes effective neutralization of gastric contents? Am. J. Digest. Dis. **6**: 127, 1939.
(b) Gill, A. M., and Keeler, C. A.: Pepsin inactivation in ulcer therapy, Brit. M. J. **2**: 194, 1943.
12. Friedenwald, J., and Morrison, S.: Use of gastric antacids, J. A. M. A. **108**: 879, 1937.
13. Berk, J. E., Rehfuss, M. E., and Thomas, J. E.: In situ effects of antacids in duodenal ulcer, Arch. Int. Med. **72**: 46, 1943.
14. Loevenhart, A. S., and Crandall, L. A.: Calcium carbonate in the treatment of gastric hyperacidity syndrome and in gastric and duodenal ulcer, J. A. M. A. **88**: 1557, 1927.
15. Kirsner, J. B., and Palmer, W. L.: The effect of various antacids on the hydrogen-ion concentrations of the gastric contents, Am. J. Digest. Dis. **7**: 85, 1940.
16. Kirsner, J. B.: The effect of calcium carbonate, aluminum phosphate and aluminum hydroxide on mineral excretion in man, J. Clin. Investigation **22**: 47, 1943.
17. Kirsner, J. B.: A study of alkalosis with special reference to the electrolyte composition of the blood serum and the role of the kidney, Ph.D. Thesis, Div. Biological Sciences, University of Chicago, 1942.
18. (a) Greenwald, I.: Gastric antacids which cannot act as systemic alkalis, Proc. Soc. Exper. Biol. and Med. **20**: 436, 1923.
(b) Shattuck, H. F., Rohdenburg, E. L., and Booher, L. E.: Antacids in the medical management of peptic ulcer, J. A. M. A. **82**: 200, 1924.
19. Brown, E. A.: The laboratory and clinical evaluation of a new antacid preparation, Ohio State M. J. **45**: 875, 1949.

20. (a) Wosika, P. H., and Emery, E. S., Jr.: The value of powdered milk and alkali for neutralizing the gastric acidity of patients with peptic ulcer, Arch. Int. Med. **9**: 1078, 1936.
(b) Wosika, P. H.: The control of gastric acidity in peptic ulcer by alkalinized powdered skimmed milk tablets, Am. J. M. Sc. **195**: 676, 1938.
21. Davies, R. E., and Longmuir, N. M.: Production of ulcers in isolated frog gastric mucosa, Biochem. J. **42**: 621, 1948.
22. Crohn, B. B.: The clinical use of colloidal aluminum hydroxide as a gastric antacid, J. Lab. and Clin. Med. **14**: 610, 1929.
23. Einsel, I. H., Adams, W. L., and Myers, V. C.: Aluminum hydroxide in the treatment of peptic ulcer, Am. J. Digest. Dis. **1**: 513, 1934.
24. Adams, W. L., Einsel, I. H., and Myers, V. C.: Aluminum hydroxide as an antacid in peptic ulcer, Am. J. Digest. Dis. **3**: 112, 1936–37.
25. Bennett, T. I., and Gill, A. M.: Colloidal aluminum hydroxide in the treatment of peptic ulcer, Lancet **1**: 500, 1939.
26. Rutherford, R. B., and Emery, E. S., Jr.: The clinical effect of colloidal aluminum hydroxide on patients with peptic ulcer, New England J. Med. **220**: 407, 1939.
27. Wilkinson, S. A., and Comanduras, P. D.: The treatment of peptic ulcer with aluminum hydroxide: a two year study, New England J. Med. **223**: 972, 1940.
28. Collins, E. N., Pritchett, C. P., and Rossmiller, H. R.: The use of aluminum hydroxide in the treatment of peptic ulcer, J. A. M. A. **116**: 109, 1941.
29. Ivy, A. C., Terry, L., Fauley, G. B., and Bradley, W. B.: The effect of administration of aluminum preparations on the secretory activity and gastric acidity of the normal stomach, Am. J. Digest. Dis. **3**: 879, 1936–37.
30. Komarov, S. A., and Komarov, O.: The precipitability of pepsin by colloidal aluminum hydroxide, Am. J. Digest. Dis. **7**: 166, 1940.
31. Warren, I. A., Front, J., and Kirsner, J. B.: The effect of antacid therapy on the peptic activity of gastric juice in man, Gastroenterology **1**: 102, 1943.
32. Kirsner, J. B.: The effect of aluminum hydroxide on the acid-base balance and on renal function, Am. J. Digest. Dis. **8**: 160, 1941.
33. Smith, F. H.: Non-reactive aluminum hydroxide in the treatment of peptic ulcer, Gastroenterology **8**: 494, 1947.
34. Fauley, G. B., Freeman, S., Ivy, A. C., and Atkinson, A. J.: Aluminum phosphate in the therapy of peptic ulcer, Arch. Int. Med. **67**: 563, 1941.
35. (a) Johnson, E. H., and Duncan, J.: The chemical testing of antacids, Quart. J. Pharm. and Pharmacol. **18**: 251, 1945.
(b) Batterman, R. C., and Ehrenfeld, I.: The ambulant treatment of the peptic ulcer syndrome: The comparative effectiveness and constipating action of antacids, Gastroenterology **9**: 141, 1947.
36. (a) Krantz, J. C., Kibler, D. V., and Bell, F. K.: The neutralization of gastric acidity with basic aluminum aminoacetate, J. Pharmacol. and Exper. Therap. **82**: 247, 1944.
(b) Reuling, J. R., Rossien, A. X., and Wolgel, M. I.: A report on peptic ulcer therapy using a new antacid, Rev. Gastroenterol. **16**: 856, 1949.
37. Haynes, H. G.: Basic aluminium carbonate as an antacid, Pharm. J. **157**: 154, 1946.
38. Mutch, N.: Synthetic magnesium trisilicate, Brit. M. J. **1**: 205, 1936.
39. Mann, W. N.: Experiments on the neutralization of HCl by magnesium trisilicate, Guy's Hosp. Rep. **87**: 151, 1937.
40. Kraemer, M.: The use of hydrated magnesium trisilicate in peptic ulcer, Am. J. Digest. Dis. **5**: 422, 1938–39.
41. Reid, C. G.: The control of gastric hyperacidity by magnesium trisilicate, Am. J. Digest. Dis. **6**: 267, 1939.
42. Kirsner, J. B.: A further study of the effect of various antacids on the hydrogen-ion concentration of the gastric contents, Am. J. Digest. Dis. **8**: 53, 1941.

43. Nicol, B. M.: Control of gastric acidity in peptic ulcer, Lancet **2**: 881, 1939.
44. Mutch, N.: Antipeptic and antacid therapy with special reference to adsorbent complexes of calcium and magnesium phosphates, Lancet **1**: 859, 1949.
45. (a) Wyllie, D.: The influence of certain antacids on the acidity of human gastric juice with special reference to magnesium trisilicate, Edinburgh M. J. **47**: 336, 1940.
(b) Goldstein, H. I.: The use of magnesium trisilicate, colloidal kaolin and aluminum hydroxide in antacid gastric therapy, J. Internat. Coll. Surgeons **2**: 379, 1939.
46. Duden, C. W., and Abel, O., Jr.: A study of the action of various neutralizing agents on gastric acidity, Rev. Gastroenterol. **7**: 334, 1940.
47. Jankelson, I. R.: Colloidal aluminum hydroxide gel and magnesium hydroxide in the management of peptic ulcer, Am. J. Digest. Dis. **14**: 11, 1947.
48. Astrup, T., and Moller, V.: Gastric antacids with retarded action, Acta pharmacol. et toxicol. **4**: 130, 1948.
49. Brick, I. B.: Experience with sodium carboxy-methylcellulose as an antacid, Am. J. Digest. Dis. **16**: 315, 1949.
50. (a) Necheles, H., Kroll, H., Bralow, S. P., and Spellberg, M. A.: Peptic ulcer in man. Part 4. A new antacid made to meet requirements of antacid therapy. Chemical and laboratory work, Am. J. Digest. Dis. **18**: 1, 1951.
(b) Bralow, S. P., Spellberg, M. A., Kroll, H., and Necheles, H.: Peptic ulcer in man. Part 5. A new antacid, SCMC, made to meet requirements of antacid therapy. Clinical evaluation, Am. J. Digest. Dis. **18**: 7, 1951.
51. Palmer, W. L.: Fundamental difficulties in the treatment of peptic ulcer, J. A. M. A. **101**: 1604, 1933.
52. Fogelson, S. J.: Gastric mucin treatment for peptic ulcer, Arch. Int. Med. **55**: 7, 1935.
53. Code, C., Ratke, H., Livermore, G., Jr., and Lundberg, W.: Occurrence of gastric secretory inhibitor activity in fresh gastric and salivary mucin, Federation Proc. **8**: 26, 1949.
54. Hardt, L. L., and Brodt, L. P.: Aluminum hydroxide and magnesium trisilicate plus mucin in treatment of peptic ulcer, Arch. Surg. **42**: 884, 1947.
55. Kammerling, E. M., and Steigmann, F.: Gastric secretory studies with a mucin-antacid mixture, Am. J. Digest. Dis. **14**: 381, 1947.
56. Littman, A.: The action of antacids in the human stomach; results with zirconium phosphate, Master's Thesis, Dept. Clinical Science, 1948, University of Illinois, Chicago.
57. Breuhaus, H. C., Akre, O. H., and Eyerly, J. B.: Nocturnal gastric secretion in normal and duodenal ulcer patients on various forms of therapy, Gastroenterology **16**: 172, 1950.
58. Winkelstein, A.: A new therapy of peptic ulcer: continuous alkalinized milk drip into the stomach, (a) Tr. Am. Gastroent. A. **35**: 176, 1932; (b) Am. J. M. Sc. **185**: 695, 1933.
59. (a) Woldman, E. E., and Rowland, V. C.: A new technique for the continuous control of the acidity in peptic ulcer by the aluminum hydroxide drip, Am. J. Digest. Dis. **2**: 733, 1935–36.
(b) Clark, A. M.: Continuous drip treatment of peptic ulcer, Lancet **1**: 435, 1950.
60. Cornell, A., Hollander, F., and Winkelstein, A.: The efficacy of the drip method in the reduction of gastric acidity, Am. J. Digest. Dis. **9**: 332, 1942.
61. Samis, S. M., and Hollander, F.: Acid-neutralizing power of several protein hydrolysates and other substances used in ulcer therapy, Gastroenterology **12**: 665, 1949.
62. Levy, J. S.: (a) The comparative buffering capacity of intact and predigested protein, Gastroenterology **11**: 883, 1948. (b) Comparative buffering capacity of intact and predigested protein following hourly feedings, Gastroenterology **16**: 370, 1950.
63. Woldman, E., Fishman, D., Knowlton, R. S., Ronsuick, A. A., and Stover, W. C.: Evaluation of protein hydrolysate therapy for peptic ulcer, J. A. M. A. **137**: 1289, 1948.
64. Feller, J., and Tidmarsh, C. J.: The effect of amino acids on gastric acidity, Canad. M. A. J. **57**: 23, 1947.

65. Rossien, A. X.: An evaluation of the antacid activity of protein hydrolysate using graduated doses in the human stomach, Am. J. Digest. Dis. **14**: 205, 1947.
66. Rafsky, H. A., Krieger, C. I., and Honig, L. J.: Protein studies in peptic ulcer, Gastroenterology **16**: 358, 1950.
67. Lopusniak, M. S., and Berk, J. E.: The comparative effects of casein hydrolysate, milk and milk-cream on gastric and duodenal bulb acidity in duodenal ulcer patients, Gastroenterology **11**: 891, 1948.
68. Sun, D. C. H., and Machella, T. E.: The effect of protein hydrolysate solutions on gastric acidity of peptic ulcer patients, Gastroenterology **16**: 576, 1950.
69. Steigmann, F., Zweig, M., and Meyer, K.: Gastric acidity response during the intravenous administration of protein hydrolysates, J. Lab. and Clin. Med. **33**: 1627, 1948.
70. Sharick, P. R., and Campbell, D. A.: Gastric secretory response to intravenously administered amino acid mixture, Surgery **27**: 396, 1950.
71. Adams, B. A., and Holmes, E. L.: Absorptive properties of synthetic resins. Part I, J. Soc. Chem. Ind. **54**: 1–6T, 1935.
72. Segal, H. L., Hodge, H., and Watson, J. S.: A polyamine-formaldehyde resin. I. Its effect upon the pH of acidified solutions and the pH and pepsin of gastric juice in vitro. II. Its toxicity in rats, Gastroenterology **4**: 484, 1945.
73. Kraemer, M., and Lehman, D.: The treatment of peptic ulcer with anion exchange resins, Gastroenterology **8**: 202, 1947.
74. Kraemer, M., and Siegel, L.: Synthetic resin—a new antacid for treatment of peptic ulcer, Arch. Surg. **56**: 318, 1948.
75. Marks, J. A.: An anion exchange resin for the medical management of peptic ulcer, Rev. Gastroenterol. **16**: 82, 1949.
76. Martin, G. J., and Wilkinson, J.: The neutralization of gastric acidity with anion exchange resins, Gastroenterology **6**: 315, 1946.
77. Wilkinson, J., and Martin, G.: Physico-chemical aspects of the action of anion exchange resins in biochemical systems, Arch. Biochem. **10**: 205, 1946.
78. Spears, M. M., and Pfeiffer, M.: Anion exchange resin and peptic ulcer pain, Gastroenterology **8**: 191, 1947.
79. Wirts, C. W., Jr., and Rehfuss, M. E.: A study of the effect of an anion exchange resin on gastric and duodenal secretions and gastric emptying, J. Clin. Investigation **29**: 37, 1950.
80. Steigmann, F., and Schlesinger, R. B.: A resin-gastric mucin mixture in the medical management of peptic ulcer, Am. J. Digest. Dis. **17**: 361, 1950.
81. Hall, A. A., and Hornisher, C. J.: The effect of anion exchange resin on the healing time of duodenal ulcer craters, Gastroenterology **16**: 181, 1950.
82. Kirsner, J. B., and Wolff, R. A.: Effect in vitro of various detergents on peptic activity of human gastric content, Gastroenterology **2**: 270, 1944.
83. Kirsner, J. B., and Spitzer, E. H.: Further studies of the effect of sodium alkyl sulfate on peptic activity, Gastroenterology **2**: 348, 1944.
84. Shay, H., Komarov, S. A., Siplet, H., and Gruenstein, M.: An evaluation of some antacid and antipeptic agents in the prevention of gastric ulceration in the rat, Am. J. Digest. Dis. **14**: 99, 1947.
85. Alpert, S., and Martin, G. J.: A comparative study of the inhibitory action of chemical agents on peptic activity, Am. J. Digest. Dis. **16**: 10, 1949.
86. Shoch, D., and Fogelson, S. J.: Studies on peptic inhibition, (a) Proc. Soc. Exper. Biol. and Med. **50**: 304, 1942; (b) Quart. Bull., Northwestern Univ. M. School, 1942.
87. Shay, H., Komarov, S. A., and Siplet, H.: The inhibitory effect of sodium dodecyl sulfate upon the gastric secretory response to histamine, Science **105**: 128, 1947.
88. Kirsner, J. B., and Wolff, R. A.: Effect of sodium alkyl sulfate on peptic activity of gastric contents in man and in vitro, Proc. Soc. Exper. Biol. and Med. **54**: 11, 1943.

89. Steigmann, F., and Marks, A. R.: Inhibition of peptic activity in the treatment of peptic ulcer, Am. J. Digest. Dis. **11**: 173, 1944.
90. Kirsner, J. B., and Wolff, R. A.: The effect of sodium alkyl sulfate on the peptic activity of the gastric contents and on the healing of gastric ulcer in man, Gastroenterology **2**: 93, 1944.
91. Breitwieser, E. R.: The effect in vivo of sodium alkyl sulfate on peptic activity, Gastroenterology **9**: 81, 1947.
92. Biguria, F., and Canzanelli, A.: The effect of continued oral administration of histamine and pancreatin on gastric secretion, Am. J. Physiol. **110**: 243, 1934.
93. Atkinson, A. J., and Ivy, A. C.: The action of histaminase on gastric secretory response to histamine and to a meal, Am. J. Physiol. **107**: 168, 1934.
94. Necheles, H., Olson, W. H., and Scruggs, W.: Histaminase: an experimental study, Am. J. Digest. Dis. **8**: 217, 1941.
95. Atkinson, A. J., Ivy, A. C., and Bass, V.: The effect of histaminase on the gastric secretory response to histamine, Am. J. Physiol. **132**: 51, 1941.
96. Grossman, M. I., and Robertson, C. R.: Inhibition by histaminase of gastric secretion in dogs, Am. J. Physiol. **153**: 447, 1948.
97. Sangster, W., Grossman, M. I., and Ivy, A. C.: The effect of two new histamine antagonists (benadryl and compound 63) on histamine-stimulated gastric secretion in the dog, Gastroenterology **6**: 436, 1946.
98. Friesen, S. R., Baronofsky, I. D., and Wangensteen, O. H.: Benadryl fails to protect against histamine-provoked ulcers, Proc. Soc. Exper. Biol. and Med. **63**: 23, 1946.
99. Lehmann, J., and Stefko, P. L.: The action of thephorin upon histamine-induced gastric secretion in dogs and on gastric ulcer formation in rats, J. Lab. and Clin. Med. **34**: 372, 1949.
100. McGavack, T. H., Elias, H., and Boyd, L. J.: The influence of benadryl on gastric acidity, Gastroenterology **6**: 439, 1946.
101. Alsted, G.: Effect of amidryl on the gastric secretions in peptic ulcer, Nord. med. **40**: 1778, 1948.
102. Kay, A. W., Scott, L. D. W., and Smith, W. E.: Observations on the use of benadryl in duodenal ulcer, Glasgow M. J. **28**: 145, 1947.
103. Moersch, R. U., Rivers, A. B., and Morlock, C. G.: Some results of the gastric secretory response of patients having duodenal ulcer noted during the administration of benadryl, Gastroenterology **7**: 91, 1946.
104. Perry, E. L., and Horton, B. T.: Use of pyribenzamine in prevention of histamine-induced gastric acidity and headache and in treatment of hypersensitiveness to cold, Am. J. M. Sc. **214**: 553, 1947.
105. Hartman, S. A., and Moore, D. M.: The effect of tripelennamine hydrochloride (pyribenzamine) on the gastric acidity of patients with peptic ulcer, Am. J. Digest. Dis. **15**: 271, 1948.
106. Emmelin, W., and Frost, J.: The effect of β-dimethylaminoethyl benzhydryl ether hydrochloride on histamine-induced gastric secretion in the cat, Acta physiol. Scandinav. **13**: 75, 1947.
107. Gilg, E.: The effect of benadryl on the secretions of gastric juice, Acta pharmacol. et toxicol. **4**: 81, 1948.
108. Ashford, C. A., Heller, H., and Swart, G. A.: The effect of antihistamine substances on gastric secretion in man, Brit. J. Pharmacol. **4**: 157, 1949.
109. (a) Cahan, A. M., Meilman, E., and Jacobson, B. M.: Agranulocytosis following pyribenzamine: report of a case, New England J. Med. **241**: 865, 1949.
(b) Hilker, A. W.: Agranulocytosis from tripelennamine (pyribenzamine) hydrochloride, J. A. M. A. **143**: 741, 1950.
(c) Maitland, H. S., Jr., and Guck, I. K.: Agranulocytosis after antihistaminic therapy, J. A. M. A. **143**: 742, 1950.

110. (a) Ivy, A. C., and Gray, J. S.: Enterogastrone, Symposia on Quantitative Biology **5**: 405, 1937.
(b) Grossman, M. I.: Gastrointestinal hormones, Physiol. Rev. **30**: 33, 1950. (These two papers summarize the experimental data.)
111. Friedman, M. H. F.: Enterogastrone and urogastrone in peptic ulcer, *in* Postgraduate Gastroenterology, H. L. Bockus, ed., 1950, W. B. Saunders Co., Philadelphia, p. 156.
112. (a) Uvnäs, B.: The effect of enterogastrone on the gastric secretions of the cat stimulated by continuous administration of histamine, Acta physiol. Scandinav. **15**: *2*, 1948.
(b) Howat, H. T., and Schofield, B.: A double histamine test for inhibitors of gastric secretion, J. Physiol. **107**: 30P, 1948.
113. Kirsner, J. B., Levin, E., and Palmer, W. L.: Studies on the nocturnal and 24-hour gastric secretions during the injection of an enterogastrone concentrate in man, Gastroenterology **10**: 256, 1948. (The gastric secretory studies in animals are summarized in this paper.)
114. Levin, E., Kirsner, J. B., and Palmer, W. L.: Preliminary observations on histamine and insulin stimulated gastric secretions during the injection of an enterogastrone concentrate in man, Gastroenterology **10**: 274, 1948.
115. Kirsner, J. B., Levin, E., and Palmer, W. L.: Effect of dialyzed enterogastrone upon twelve-hour nocturnal gastric secretions in man, Proc. Soc. Exper. Biol. and Med. **70**: 685, 1949.
116. Ferayorni, R. R., Code, C. F., and Morlock, C. G.: The effect of enterogastrone concentrates on gastric secretions in human beings, Gastroenterology **11**: 730, 1948.
117. Pollard, H. M., Block, M., Bachrach, W. H., and Mason, J.: Treatment of peptic ulcer with enterogastrone, Arch. Surg. **56**: 372, 1948.
118. Ivy, A. C., Littman, A., and Grossman, M. I.: Recurrence of peptic ulcer in man as affected by treatment with an enterogastrone preparation, Gastroenterology **12**: 735, 1949.
119. (a) Surkes, A. W.: Medical treatment of gastric and duodenal ulcer with robuden, Schweiz. med. Wchnschr. **77**: 455, 1947.
(b) Mamie, M.: Traitement de l'ulcère gastroduodenale par le Robuden, Gastroenterologia **73**: 157, 1948.
(c) Neumann, H.: Treatment of early and late cases of peptic ulcer, Schweiz. med. Wchnschr. **78**: 1085, 1948.
(d) Olloqui, F. F.: Treatment of peptic ulcers: results obtained with extracts of stomach and small intestine, Rev. españ. enferm. ap. Digest. y nutrición **9**: 444, 1950.
(e) Stolte, J. B.: Therapeutic experiment in peptic ulcer, Lancet **2**: 858, 1950.
120. (a) Wieczorowski, E., Gray, J. S., and Ivy, A. C.: The effect of urogastrone on gastric secretions in man, Am. J. Physiol. **129**: 496, 1940.
(b) Gray, J. S., Wieczorowski, E., and Ivy, A. C.: Inhibition of gastric secretion in man with urogastrone, Am. J. Digest. Dis. **8**: 365, 1941.
(c) Gray, J. S.: The present status of urogastrone, Am. J. Digest. Dis. **8**: 365, 1941.
121. (a) Sandweiss, D. J., Saltzstein, H. C., and Farbman, A. A.: The relation of sex hormones to peptic ulcer, Am. J. Digest. Dis. **6**: 6, 1939.
(b) Friedman, M. H. F., and Sandweiss, D. J.: The gastric secretory depressant in urine, Am. J. Digest. Dis. **8**: 366, 1941.
(c) Sandweiss, D. J.: Enterogastrone, anthelone, and urogastrone, Gastroenterology **5**: 404, 1945.
(d) Sandweiss, D. J.: The status of hormones in peptic ulcer, *in:* Peptic ulcer, diagnosis and treatment, W. B. Saunders Co., Philadelphia. To be published.
122. Abrahamson, R. H., Church, R., and Hinton, J. W.: Hormonal effects on the gastroduodenal mucosa, Am. J. M. Sc. **204**: 809, 1942.
123. Strauss, M. B., and Castle, W. B.: Studies of anemia in pregnancy. I. Gastric secretion in pregnancy and the puerperium, Am. J. M. Sc. **184**: 655, 1932.

124. Way, S.: Relations between gastric acidity and the anterior pituitary-like hormone content of urine in pregnant women, Brit. M. J. **2**: 182, 1945.

125. Culmer, C. V., Atkinson, A. J., and Ivy, A. C.: The depression of gastric secretions by the anterior pituitary-like fractions of pregnancy urine, Endocrinology **24**: 631, 1939.

126. (a) Sandweiss, D. J., Saltzstein, H. C., and Farbman, A. A.: The prevention or healing of experimental peptic ulcer in Mann-Williamson dogs with the anterior pituitary-like hormone antuitrin-S, Am. J. Digest. Dis. **5**: 24, 1938.

(b) Sandweiss, D. J., and Friedman, M. H. F.: The use of urine extracts in the treatment of ulcer, Am. J. Digest. Dis. **7**: 50, 1940.

(c) Sandweiss, D. J., Sugarman, M. H., Friedman, M. H. F., Saltzstein, H. C., and Farbman, A. A.: The effect of urine extracts on peptic ulcer: an experimental and clinical study, Am. J. Digest. Dis. **8**: 371, 1941.

(d) Broad, G. G., and Berman, L. G.: Treatment of experimental Mann-Williamson ulcers with anterior pituitary-like hormone (antuitrin-S), Am. J. Digest. Dis. **8**: 27, 1941.

(e) Saltzstein, H. C., Sandweiss, D. J., Hill, E. J., and Hammer, J.: Results in treatment of 374 Mann-Williamson dogs, Gastroenterology **12**: 122, 1949.

127. Manville, I. A., and Munroe, W. R.: On the inhibitory effect of corpus luteum (progesterone) on gastric secretion, Am. J. Digest. Dis. **3**: 482, 1936–37.

128. Atkinson, A. J., and Ivy, A. C.: Further attempts to produce achlorhydria, Am. J. Digest. Dis. **5**: 30, 1938–39.

129. Schiff, L., and Felson, H.: The effect of estrogenic hormone on gastric acidity, Am. J. Digest. Dis. **5**: 292, 1938–39.

130. Winkelstein, A.: A possible relationship between the ductless glands secreting the sex hormones and peptic ulcer, J. Mt. Sinai Hosp. **7**: 29, 1942.

131. Kirsner, J. B., Levin, E., and Palmer, W. L.: Failure of an extract of pregnant mares' urine to influence gastric secretions in man, Proc. Soc. Exper. Biol. and Med. **69**: 108, 1948.

132. Tomenius, J.: On the relation between urogastrone and chorionic gonadotropin. An investigation of the effect of chorionic gonadotropin upon gastric secretion, Gastroenterology. To be published.

133. Kirsner, J. B., Levin, E., and Palmer, W. L.: Effect of various hormones on gastric secretion of patients with duodenal ulcer. To be published.

134. (a) Babkin, B. P., Komarov, O., and Komarov, S. A.: The effect of activated ergosterol and of parathyroid hormone on gastric secretion in the dog, Endocrinology **26**: 703, 1940.

(b) Babkin, B. P.: The effect of parathyroid hormone and of activated ergosterol on gastric secretion in the dog, Rev. Gastroenterol. **7**: 373, 1940.

135. Levy, M. M., and Levy, E.: Parathyroid extract in the treatment of gastroduodenal ulcer, Arch. d. mal. de l'app. digestif **21**: 916, 1931.

136. Spiro, H. M., Reifenstein, R. W., and Gray, S. J.: The effect of adrenocorticotropic hormone upon uropepsin excretion, J. Lab. and Clin. Med. **35**: 899, 1950.

137. (a) Sandweiss, D. J., Saltzstein, H. C., Scheinberg, S. R., and Parks, A.: Hormone studies in peptic ulcer, J. A. M. A. **144**: 1436, 1950.

(b) Smyth, G. A.: Activation of peptic ulcer during pituitary adrenocorticotropic hormone therapy, J. A. M. A. **145**: 474, 1951.

(c) Kirsner, J. B., and Klotz, A. P.: The harmful effects of ACTH and cortisone in gastric ulcer. To be published.

138. (a) Grimson, K. S., Chittum, J. H., and Longino, F. H.: Comparison of effects of a new ganglionic blocking agent and a new sympatholytic, Federation Proc. **8**: 61, 1949.

(b) Cook, D. L., Hambourger, W. E., and Bianch, R. G.: Pharmacology of a new autonomic blocking agent, 2,6 dimethyl-1, 1-diethyl piperdinium bromide (Sc 1950), J. Pharmacol. and Exper. Therap. **99**: 435, 1950.

139. Ivy, A. C., Grossman, M. I., and Bachrach, W. H.: Peptic ulcer, 1950, The Blakiston Co., Philadelphia. (The literature on atropine is summarized in detail.)

140. Atkinson, A. J., and Ivy, A. C.: Studies on the control of gastric secretions. I. Drugs acting on the autonomic-sympathetic system. II. Drugs acting as central emetics, Am. J. Digest. Dis. **4**: 811, 1937–38.

141. Levin, E., Kirsner, J. B., and Palmer, W. L.: The variable effect of atropine sulfate on fasting gastric secretion in man, J. Lab. and Clin. Med. **37**: 415, 1951. (The previous studies in man are briefly summarized in this paper.)

142. Mears, F. B.: The effect of atropine on gastric secretion during the night, Surgery **13**: 214, 1943.

143. Rafferty, M. A., Van Liere, E. J., and Sleeth, C. K.: The effect of ephedrine on the secretions of acid by the human stomach, Am. J. Digest. Dis. **4**: 366, 1937–38.

144. Higgins, J. R., Schoen, A. M., and Knoefel, P. K.: The effects of some synthetic antispasmodic agents on human gastric and duodenal functions, Gastroenterology **11**: 508, 1948.

145. (a) Tilford, C. H., Van Campen, M. G., Jr., and Shelton, R. S.: Amino esters of substituted alicyclic carboxylic acids, J. Am. Chem. Soc. **69**: 2902, 1947.

(b) Chamberlin, D. T.: Clinical application of bentyl hydrochloride. A new antispasmodic, Gastroenterology **17**: 224, 1951.

146. Lorber, S. H., and Machella, T. E.: The effect of syntropan on the motor activities of the human gastrointestinal tract and on gastric acidity, Gastroenterology **12**: 57, 1949.

147. Clark, B. B.: A comparison of the effect on gastric secretions of syntropan, demerol, and trasentine with atropine, Gastroenterology **9**: 454, 1947.

148. Brown, H. S., Posey, E. L., Jr., and Gambill, E. E.: Studies of the effect of TEAC on gastric motor and secretory functions in patients with duodenal ulcer, Gastroenterology **10**: 837, 1948.

149. Dodds, D. C., Ould, C. L., and Dailey, M. E.: The effect of tetraethylammonium chloride on gastric motility in man, Gastroenterology **10**: 1007, 1948.

150. Zweig, M., Steigmann, F., and Meyer, K. A.: The effect of TEAC on gastric motility and on unstimulated and histamine-stimulated gastric secretion, Gastroenterology **11**: 200, 1948.

151. Cayer, D., Little, J. M., and Yeagley, J.: The use of tetraethylammonium chloride in the treatment of patients with peptic ulcer, Gastroenterology **12**: 219, 1949.

152. Neligh, R. B., Holt, J. F., Lyons, R. H., Hoobler, S. W., and Moe, G. K.: Effects of TEAC on the human gastrointestinal tract, Gastroenterology **12**: 275, 1949.

153. Ferrer, J. M.: The effect of tetraethylammonium chloride on gastric secretion and acidity in peptic ulcer, Surg., Gynec. and Obst. **87**: 76, 1948.

154. (a) Paton, W. D. M., and Zaimis, E. J.: The pharmacological actions of polymethylene bistrimethyl-ammonium salts, Nature, London **162**: 810, 1948; Brit. J. Pharmacol. **4**: 381, 1949.

(b) MacDonald, I. R., and Smith, A. N.: Effect of tetraethylammonium bromide on gastric secretion and motility, Brit. M. J. **2**: 620, 1949.

155. Graham, A. J. P.: Toxic effects in animals and man after tetraethylammonium bromide, Brit. M. J. **2**: 321, 1950.

156. (a) Kay, A. W., and Smith, A. N.: Effect of hexamethonium iodide on gastric secretion and motility, Brit. M. J. **1**: 460, 1950.

(b) Kay, A. W., and Smith, A. N.: Effect of oral hexamethonium salts on gastric secretion, Brit. M. J. **2**: 807, 1950.

(c) Douthwaite, A. H., and Thorne, M. G.: The effects of hexamethonium bromide on the stomach, Brit. M. J. **1**: 111, 1951.

157. Scott, L. D. W., Kay, A. W., O'Hare, M. M., and Simpson, J. A.: Hexamethonium bromide in duodenal ulcer, Brit. M. J. **2**: 1470, 1950.

158. Hambourger, W. E., Cook, D. L., Winbury, M. M., and Freese, L. T. B.: Pharmacology of β-diethylamino ethyl xanthene-9-carboxylate methobromide (banthine) and chloride, J. Pharmacol. and Exper. Therap. In press.

159. Longino, F. H., Grimson, K. S., Chittum, J. R., and Metcalf, B. H.: An orally effective quaternary amine, banthine, capable of reducing gastric motility and secretions, Gastroenterology **14**: 301, 1950.

160. Smith, C. A., Woodward, E. R., Janes, C. W., and Dragstedt, L. R.: The effect of banthine on gastric secretions in man and experimental animals, Gastroenterology 15: 718, 1950.

161. Levin, E., Kirsner, J. B., and Palmer, W. L.: The effect of banthine on gastric secretion in man. To be published.

162. Benjamin, F. B., Rosiere, C. E., and Grossman, M. I.: A comparison of the effectiveness of banthine and atropine in depressing gastric acid secretions in man and the dog, Gastroenterology **15**: 727, 1950.

163. Walters, R. L., Morgan, J. A., and Beal, J. M.: Effects of β-diethyl-aminoethyl xanthene-9-carboxylate methobromide (banthine) on human gastrointestinal functions, Proc. Soc. Exper. Biol. and Med. **74**: 526, 1950.

164. Asher, L. M.: Gastroscopic observations on the effect of banthine on the human stomach, Gastroenterology. To be published.

165. (a) Grimson, K. S.: Clinical trial of banthine in cases of peptic ulcer (comment), Gastroenterology **14**: 583, 1950.

(b) Grimson, K. S., Lyons, C. K., and Reeves, R. J.: Clinical trial of banthine in 100 patients with peptic ulcers, J. A. M. A. **143**: 873, 1950.

166. Brown, C. H., and Collins, E. N.: The use of banthine in the treatment of duodenal ulcer, Gastroenterology. To be published.

167. Winkelstein, A.: Banthine in the therapy of peptic ulcer, Correspondence to the Editor, J. A. M. A. **144**: 1501, 1950.

168. Lorber, S. H.: Inhibition of gastric secretions in ulcer patients with dibutoline, Postgraduate gastroenterology, 1950, H. L. Bockus, ed., W. B. Saunders Co., Philadelphia, p. 34.

169. Levin, E., Kirsner, J. B., and Palmer, W. L.: Effect of dibuline on nocturnal gastric secretion in man, Proc. Soc. Exper. Biol. and Med. **72**: 213, 1949.

170. (a) Kirsner, J. B., Levin, E., and Palmer, W. L.: The effect of some newer cholinergic blocking agents upon basal gastric secretion in patients with duodenal ulcer. To be published.

(b) Margolin, S., Doyle, M., Giblin, J., Makovsky, A., Spoerlein, M. T., Stephens, L., Berchtold, H., Belloff, G., and Tislow, R.: Pharmacological properties of a new parasympathetic blocking agent, N,N dimethyl 4-piperdylidene 1,1 diphenylmethane methyl sulfate (Prantal). To be published.

171. (a) Olmsted, J. M. D., and Giragossiwitz, G.: Some effects of amytal anesthesia, J. Lab. and Clin. Med. **16**: 354, 1930.

(b) Coffey, R. J., Koppanyi, T., and Linegar, E. R.: The effect of barbiturates on digestive secretion, Am. J. Digest. Dis. **7**: 21, 1940.

172. Noble, C. L.: The stimulation and inhibition of gastric secretion in cats by barbiturate and thiourea derivatives, Canad. M. A. J. **60**: 55, 1949.

173. Merendino, K.: Pharmacological aspects of gastric secretion. I. The effect of opium alkaloids and an allied drug demerol on pouch secretion in dogs. II. The production of "peptic" ulcer in guinea pigs and cats with morphine sulphate alone and combined with fractures. III. The question of tolerance in the gastric secretory response of pouch dogs to prolonged administration of morphine sulphate. IV. The effect of opium alkaloids and an allied drug demerol on gastric secretion in man. V. The effect of phenobarbital on the gastric secretions in dog and man, Gastroenterology **10**: 504, 1948.

174. Levin, E., Kirsner, J. B., and Palmer, W. L.: Effect of large amounts of sodium amytal on nocturnal gastric secretion in peptic ulcer. Unpublished data.

175. (a) De Anciaes, C. J. H.: Insuline, pituitrine et sécrétion gastrique, Compt. rend. Soc. de biol. **95**: 313, 1926.

(b) Metz, M. H., and Lackey, R. W.: Peptic ulcer treated by posterior pituitary extract, Texas State J. Med. **34**: 214, 1938; Am. J. Digest. Dis. **7**: 27, 1940; South. M. J. **36**: 747, 1943.

176. (a) Fitzgerald, O., and Murphy, P.: Role of gastric urease, Nature, London **162**: 896, 1948.

(b) Fitzgerald, O., and Murphy, P.: Studies on the physiological chemistry and clinical significance of urease and urea, with special reference to the stomach, Irish J. M. Sc., Sixth Series **291**: 97, 1950.

177. (a) Brunschwig, A., Von Prohaska, J., Clarke, T. H., and Kandel, E.: A secretory depressant in gastric juice of patients with pernicious anemia, J. Clin. Investigation **18**: 415, 1939.

(b) Brunschwig, A., Rasmussen, T., Camp, E., and Moe, R.: Gastric secretory depressant in gastric juice, Surgery **12**: 887, 1942.

178. Babkin, B. P., and Karp, D.: Effect of quinine and atabrine on gastric secretion, Canad. M. A. J. **56**: 137, 1947.

179. (a) Burn, J. H., and Vane, J. R.: The inhibitory action of paludrine on the secretion of gastric juice, Brit. J. Pharmacol. **3**: 346, 1948.

(b) Vane, J. R., Walker, J. M., and Wynn Parry, C. B.: The effect of paludrine on gastric secretion in man, Brit. J. Pharmacol. **3**: 350, 1948.

(c) Doll, R., and Schneider, R.: The effect of paludrine on human gastric secretion, Brit. J. Pharmacol. **3**: 352, 1948.

A TEST FOR THE MORE ACCURATE RECOGNITION OF GALL-BLADDER AND LIVER BILE DURING DIAGNOSTIC BILIARY DRAINAGE *

By Augustus A. Hall, Colonel, M.C., F.A.C.P., *Fort Sam Houston, Texas,* and John M. Masen, Major, M.S.C., *Miami, Florida*

Introduction

The gross interpretation of gall-bladder bile and liver bile during diagnostic biliary drainage is basically important in the evaluation of the fluid obtained. The sequence of bile flow in a normal subject, as first emphasized by Lyon,[1] is a small amount of "A," or common duct bile, usually lemon to golden yellow in color. The next bile to appear is the "B" or gall-bladder bile, yellow brown in color. Last in the sequence is the "C," or liver bile, normally a golden yellow in color. Many deviations from this normal color sequence occur in disease and/or pathologic physiologic aberrations of the biliary tract. Very dark, not infrequently jet black gall-bladder bile is seen in cases of gall-bladder stasis.

Lyon [2] and Counseller and McIndoe [3] and the author have pointed out that, if the intrahepatic and extrahepatic ducts are greatly dilated, even though the gall-bladder has been removed, large quantities of very dark green, black or muddy brown bile will be recovered. In at least two cases the author has missed a drainage diagnosis of cholelithiasis because of a lack of demonstrated crystals in what appeared to be gall-bladder bile. In these two cases the gall-bladder had failed to visualize at cholecystography and, on operation, gall-stones were found in the gall-bladder of the type not opaque to roentgen-ray. This can be embarrassing. Obviously, the dark bile seen on these two occasions was unusually dark liver bile and not from the gall-bladder.

One of us (A.A.H.) has seen liver bile as dark as some gall-bladder biles in drainages performed on cholecystectomized patients. These instances, not frequent, occur just often enough to make one wonder about the accuracy of the gross identification of the two kinds of bile in the patient who still has a gall-bladder.

Accordingly, it was felt necessary to devise some laboratory procedure to check the validity and accuracy of the gross designation of gall-bladder and liver bile during diagnostic biliary drainage.

The Iodine Test

The determination of priodax (iodoalphionic acid, 51.38 per cent iodine) in the bile drainage fluid was developed by one of us (J. M. M.). The

* Received for publication August 14, 1950.
From the Brooke General Hospital, Fort Sam Houston, Texas.

principle of the method is as follows: The biliary drainage fluid containing the priodax is oxidized by boiling with acid permanganate. The organic matter is destroyed and the iodine of the priodax set free and converted to iodate (Groak reaction). On the addition of an excess of potassium iodide, the iodate oxidizes the iodide, with the liberation of free iodine according to the following reaction:

$$IO_3^- \text{ plus } 5\ I \rightleftarrows 3\ I_2 \text{ plus } H_2O$$

Addition of starch solution to this iodine-containing solution results in the formation of a blue color, which is measured in a photoelectric colorimeter or spectrophotometer and its concentration determined by comparison with a standard solution of priodax submitted to the same procedure.

Method: Reagents and apparatus—

1. Standard solution of priodax is prepared by dissolving 500 mg. of the compound in 500 c.c. of 0.5 per cent sodium hydroxide.
2. Sulfuric acid, 10 per cent by volume solution, is prepared by diluting 100 c.c. of concentrated sulfuric acid (94 to 96 per cent) to one liter with distilled water.
3. Saturated solution of potassium permanganate.
4. Stabilized starch solution. Dissolve 1 gm. of soluble starch in 100 c.c. of hot 20 per cent sodium chloride solution.
5. Potassium iodide solution, 5.0 per cent, prepared fresh each day.
6. Sodium nitrite, 10 per cent solution.
7. Urea, 30 per cent solution.
8. Test tubes, pyrex, 200 by 25 mm.
9. Electric hot plate.
10. Photoelectric colorimeter.

Technic: Place 0.05 c.c. of the standard priodax solution in a 200 by 25 mm. pyrex test tube, and in a similar tube place 0.05 c.c. of the biliary drainage fluid. To each tube add 10.0 c.c. of 10.0 per cent sulfuric acid and one drop of saturated potassium permanganate solution. The permanganate should be added in such manner that it does not strike the walls of the test tube. Add two glass beads to each tube to prevent bumping during the boiling process. Place the tubes on the hot plate and support in an upright position by means of a metal rack. Boil the samples until the volume of the fluid in the tubes has been reduced to approximately half (5.0 c.c.) the original volume. Should the permanganate become decolorized at any time during the procedure, an extra drop (or more if required) of the saturated permanganate solution is added.

Sodium nitrite is now added to the boiling sample drop by drop until all the permanganate has been decomposed and the sample is clear and colorless. It is of the utmost importance that the permanganate be completely decomposed at this step, since any undecomposed permanganate remaining

will react with the starch iodide reagent to give an intense color. The sides of the tubes are next washed down with 2.0 c.c. of distilled water, to remove any permanganate that may be adherent to the sides of the tube and to insure its complete decomposition by the nitrite. The excess nitrite is now decomposed by adding four drops of urea solution; the tubes are removed from the hot plate and swirled in such manner that contact of the walls of the tube with urea is assured. As in the case of the permanganate, it is of the utmost importance that all of the nitrite be destroyed by the urea solution, since the nitrite also reacts with the starch-iodide solution to form a blue color.

The tubes are cooled for 10 minutes in an ice bath, then diluted to 35 c.c. with distilled water and mixed by swirling. To each tube add 1.0 c.c. of the starch solution, followed by 1.0 c.c. of the potassium iodide solution. Mix thoroughly by swirling, then dilute to the 50 c.c. mark and mix by inverting. Transfer to cuvettes and obtain the optical density readings in a photoelectric colorimeter or spectrophotometer. With a colorimeter, the most satisfactory reading may be obtained with a green filter. If a spectrophotometer is used, the reading is made with the wave-length scale set to 500 mu. The scale of the instrument is set to zero density with a blank tube containing distilled water. If desired, a blank which has been subjected to the same oxidative procedure as the sample and standard may be used for setting the blank reading of the instrument.

Calculation of results:

$$\frac{\text{Reading of the unknown} \times 100}{\text{Reading of the standard}} = \text{mg. priodax per 100 c.c. of biliary drainage fluid.}$$

Note: If the instrument used for the color measurement reads "transmission" instead of "optical density," the optical density may be obtained by subtracting the logarithm of the transmission reading from two, with the blank reading set at 100 per cent transmission.

Experimental: Biliary drainage fluid obtained from patients who had not received any priodax gave no reaction for iodine when submitted to the above analytic procedure. When priodax was added to such fluid, in amounts varying from 10 mg. to 200 mg. per 100 c.c., the added priodax was recovered with a maximal error no greater than 10.0 per cent and an average error of 5.0 per cent. When the concentration of priodax was between 10 mg. and 200 mg. per 100 c.c., the color development followed Beer's law in that color was proportional to concentration, and the formula for the calculation of results as given above was valid. Above 200 mg. per 100 c.c. the deviation from the theoretic was great enough to cause too large an error. When such a fluid is encountered, the determination is repeated, using a lesser amount of the biliary drainage fluid. With most of the subjects who comprised the groups to be discussed in this report and

who had received the usual dosage of priodax, the concentration of this substance in the drainage fluid was between 10 mg. and 200 mg. per 100 c.c. An occasional fluid was encountered in which the concentration was as high as 300 mg. per 100 c.c.

The sensitivity of the method is adequate for the determination of priodax when the usual dosage of 3 gm., such as is administered for the purpose of gall-bladder visualization, is given orally. If greater sensitivity is desired for use with the smaller dosages of the drug, it may be achieved by (1) increasing the amount of fluid used for the analysis, (2) diluting the final color to a volume of 10 or 15 c.c. instead of 50 c.c., and (3) reading in the colorimeter with a red filter or at a wave length of 620 mu.

A sample of priodax assayed for its iodine content by this technic gave a value of 53.0 per cent iodine (theoretic, 51.38 per cent).

Method of Investigation

It was decided to give diagnostic biliary drainage patients six tablets of priodax orally prior to the drainage, and to determine the concentrations of iodine in the various fractions of bile by the above described method.

The first group of 13 patients was given six tablets of priodax 14 hours before their biliary drainage. Cholecystograms were made prior to the drainage and, in the first eight patients, after drainage. The stated loss of volume of the gall-bladder following biliary drainage was an estimate by the radiologist. A Lyon duodenal tube was passed to the second part of the duodenum and bile was drained using the Lyon-Meltzer technic. The duodenal residuum was designated as fraction I. The bile following each stimulation with magnesium sulfate or olive oil was designated as fractions II, III or IV. At the conclusion of the biliary drainage the fractions were tested for iodine.

Table I

Case	Cholecystogram Before Drainage Visualization	Cholecystogram After Drainage Loss of Volume (Percentage)	Fraction I			Fraction II			Fraction III			Fraction IV		
			Color	Bile	Test	Color	Bile	Test	Color	Bile	Test	Color	Bile	Test
1	Normal	25	LY	C	10.3	YB	BC	145	YB	B	154	YB	B	164
2	Normal	25	GY	C	29	GY	BC	34	YB	B	47	YB	B	34
3	Normal	50	LY	C	0	YB	BC	49	DYB	B	112			
4	Normal	25	LY	C	0	GY	BC	35	YB	BC	48.5	YB	BC	33
5	Normal	10	LY	C	10.3	LY	C	0						
6	Normal	100	GY	C	17.2	DYB	B	290	YB	B	204	YB	B	131
7	Normal	50	GY	C	30.6	PYB	BC	15	YB	BC	32	DYB	B	163
8	Normal	25	GY	C	25.9	GY	C	0	YB	B	52.9	DYB	B	193
9	Normal		LY	C	2.4	LY	C	0	GY	C	14	LY	C	4.35
10	Normal		PY	C	5.5	DGY	BC	35						
11	Elongated		LY	C	0	GY	C	0	YB	B	51			
12	Normal		GY	C	57	GY	C	33	BLB	B	215			
13	Normal		PY	C	2.4	LY	C	10.8	YB	BC	50	BLB	B	285

Color Key

L—Lemon G—Golden P—Pale D—Dark BL—Black B—Brown Y—Yellow

Test—Mg. priodax per 100 c.c. of drainage fluid.

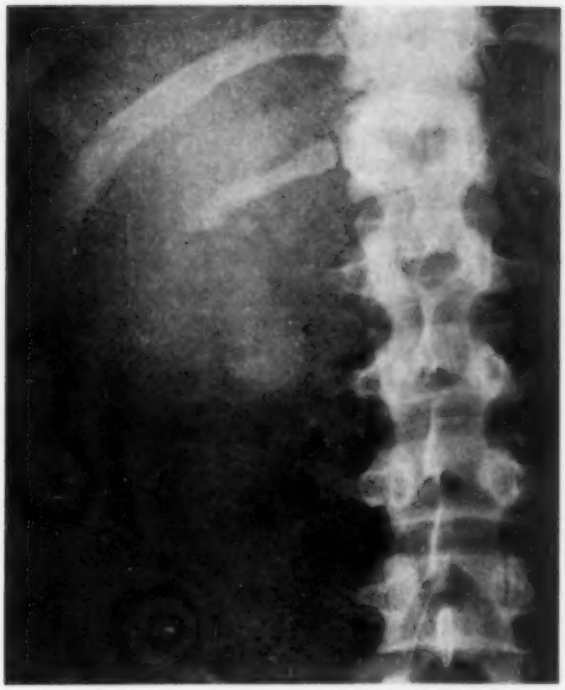
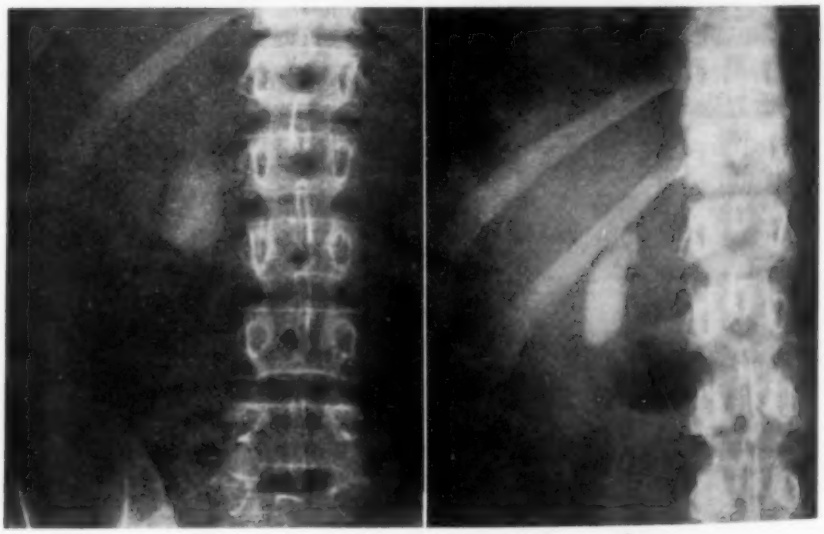


FIG. 1. Cholecystogram prior to biliary drainage of case 13 in table 1.



a *b*

FIG. 2 *a*. Cholecystogram of case 7, table 1, prior to biliary drainage.
FIG. 2 *b*. Cholecystogram of case 7, table 1, immediately after biliary drainage.

TABLE II
Cholecystectomized Patients

Case	Fraction I		Fraction II		Fraction III	
	Color	Test	Color	Test	Color	Test
1	GY	14	GY	18	Y	25
2	YB	45	LY	26.7	GY	21.7

Priodax given 14 hours prior to drainage.

The results in the group of 13 patients just described are summarized in table 1. Cholecystography was employed to assure us that the dye was present in concentrated form in the gall-bladder (figure 1). The first eight patients were also roentgen-rayed after drainage to show emptying of the gall-bladder. This varied from 10 to 100 per cent, but in none of the eight did the gall-bladder fail to lose volume (figure 2). The color of the bile was noted and the gross designation of bile recorded before testing for iodine. With the exception of fractions I and II in case 7 and fraction I in case 12, the results compared favorably with the gross designation of the bile. It was seen, however, that the liver apparently still contained dye at the end of 14 hours.

Two cholecystectomized patients were given the oral priodax 14 hours prior to drainage. Table 2 demonstrates the presence of iodine in all fractions of bile recovered.

A group of four cholecystectomized patients was given the same oral dose of priodax 38 hours prior to the biliary drainage. During the 38 hour period they were restricted to a low fat, no meat diet so as not to empty the gall tract by food. Following their drainages, their fractions of bile were tested for iodine. Table 3 shows that no iodine was detected in any of the fractions. It should be noted that three of their fractions were grossly similar in color to gall-bladder bile.

Finally, a group of nine subjects with gall-bladders was given the priodax 38 hours prior to their biliary drainages, using the same dietary

TABLE III
Cholecystectomized Patients

Case	Fraction I		Fraction II		Fraction III	
	Color	Test	Color	Test	Color	Test
1	GY	0	GY	0	GY	0
2	PY	0	GY	0	YB	0
3	YB	0	Y	0	GrB	0
4	GY	0	GY	0	GY	0

Priodax given 38 hours prior to drainage.

precautions as stated above. Table 4 shows a summary of the results in these cases. In only one instance was a false result encountered. This was in fraction II of case 6 where a specimen of blackish-brown bile designated "B," or gall-bladder bile, was negative for iodine.

TABLE IV

Case	Fraction I			Fraction II			Fraction III			Fraction IV		
	Color	Bile	Test	Color	Bile	Test	Color	Bile	Test	Color	Bile	Test
1	PY	C	0	BL.B	B	26	YB	BC	16			
2	LY	C	0	GY	C	0	YB	B	20			
3	PYB	BC	22	DYB	B	140	PYB	BC	24			
4	PY	C	0	DYB	B	26	DYB	B	26			
5	PY	C	0	BL.B	B	34	BL.B	B	65	BL.B	B	122
6	GY	C	0	BL.B	B	0	BL.B	B	23			
7	LY	C	0	YB	B	30	GY	C	0			
8	LY	C	0	YB	B	25	YB	B	30			
9	LY	C	0	LY	C	0	YB	B	24			

Priodax given 38 hours prior to drainage.
All patients had gall-bladders.

DISCUSSION

We feel the use of this test has demonstrated that, in the majority of instances, the gross designation of drained bile by a trained observer is clinically accurate and valid.

This iodine test is not advocated as a routine test during diagnostic biliary drainage. It should be used in selected cases. It is subject to the same disadvantages that obtain with cholecystography, but not to the same extent. The instances of failure in the detection of gall-bladder bile by the iodine test would probably be less than the nonvisualization by roentgen examination following the ingestion of priodax. Amounts of dye in the gall-bladder bile too slight to give a roentgen-ray shadow may possibly be detected by this method.

These conjectures and other possible uses of the test remain for future study.

SUMMARY

In some cases of diagnostic biliary drainage, liver bile may appear grossly as dark as gall-bladder bile. This gives a false diagnostic impression.

The iodine test, a laboratory procedure to aid in the more accurate gross designation of liver and gall-bladder bile, is described.

Thirteen subjects with gall-bladders were given six priodax tablets 14 hours prior to biliary drainage. All gall-bladders visualized by cholecystography, and eight were shown to have partially emptied following drainage. The iodine test was performed on all bile fractions and corresponded quite well in its concentrations to the bile designations made by the examiner. It was apparent that dye was still present in the liver at the end of 14 hours.

Two cholecystectomized patients were given priodax 14 hours prior to drainage, and iodine was detected in all fractions.

Four cholecystectomized subjects were given priodax 38 hours before drainage, and no iodine was detected in any of their bile fractions.

A group of nine subjects with gall-bladders was given priodax 38 hours prior to drainage and no iodine was detected in any fraction of bile designated grossly as "C," or liver bile. One false negative reaction was encountered with designated "B," or gall-bladder bile.

Conclusions

No conclusions can be drawn from this small series of cases. It seems that, in the majority of instances, the trained observer can satisfactorily differentiate gall-bladder from liver bile during diagnostic biliary drainage. It appears that priodax is present in the liver at the end of 14 hours but not at the end of 38 hours.

The iodine test described above is sufficiently accurate and simple to be used in clinical studies of the concentration of this substance in biliary drainage fluid.

BIBLIOGRAPHY

1. Lyon, B. B. V.: Non-surgical drainage of the gall-tract, 1923, Lea and Febiger, Philadelphia and New York.
2. Lyon, B. B. V.: The cyclopedia of medicine, surgery and specialties, 1939, F. A. Davis Co., Philadelphia, pp. 165–185.
3. Counseller, V. S., and McIndoe, A. H.: Dilatation of bile ducts (hydrohepatosis), Surg., Gynec. and Obst. **43**: 729, 1926.

ATELECTASIS OF THE RIGHT MIDDLE LOBE RESULTING FROM PERFORATION OF TUBERCULOUS LYMPH NODES INTO BRONCHI IN ADULTS *

By Abraham G. Cohen, M.D., F.A.C.P., *New York, N. Y.*

Tuberculous mediastinal lymphadenitis results from the persistence or reactivation of the infection which originates with the primary complex. Naturally, it is found most frequently in children and adolescents, but it is also common in non-Caucasian adults. Among its complications are those which result from the erosion of the caseous nodes into neighboring organs. The node becomes adherent to the bronchial wall and erodes through it as far as the lumen with varying rapidity. Typical lesions of tuberculous endobronchitis in the form of ulcers and tuberculous granulation tissue appear at the site of the perforation. The subsequent evolution of these lesions varies: they may spread, persist or heal, with or without stricture formation. The protruding node may partially or completely occlude the lumen of the bronchus and affect accordingly the aeration of corresponding portions of the lung. Subsequently the node may liquefy or sequestrate, and bronchogenic spread of the tuberculous infection to the lung may result.

In white adults, the incidence of massive caseous mediastinal lymphadenitis is rare. However, as studies by Arnstein [1, 2] and Rich [3] have shown, in aged individuals the tendency to reactivation increases as a result of diminishing resistance, the presence of pneumoconiotic changes and perhaps other factors. In these individuals, the tuberculous infection usually is of a more productive nature and hence more indolent in its behavior. Perforation into a bronchus develops more gradually and the opportunity for healing reactions to appear is greater; conversely, spread of the infection beyond the site of perforation is less frequent. An end-stage is often reached which ranges in extent from a simple scar in the bronchial mucosa to severe bronchial stenosis or deformity; evidence of the original tuberculous infection is either scanty or absent entirely.

In aged individuals, the nodes are often very anthracotic. In the course of the erosion, carbon particles gravitate through the bronchial wall as far as the mucosa, thus literally coloring the other pathologic changes. Calcification is a characteristic feature of the healing process in tuberculosis. When it occurs in a node which has perforated partially through the wall of a bronchus, the calcifications are likely to be intramural. These calcified spicules, possessing sharp edges, may act as foreign bodies and burrow

* Received for publication July 21, 1949.
From the Medical Service of the Beth Israel Hospital, New York, N. Y.

mechanically into the lumen; they are sometimes expectorated spontaneously or may be removed endoscopically, and are known as broncholiths.

Between the extremes of rapid perforation by caseous nodes and slow perforation by those less extensively or actively infected, every gradation of secondary change in the bronchus is possible. The presence or absence of calcification and anthracosis increases the complexity of the array of pathologic changes. These were well known to the older pathologists (quoted by Fleischner [4]) and have been studied more recently by Arnstein,[1, 2] Auerbach [5] and Silverman.[6]

In children and colored adults, the rapid perforation into a bronchus of a caseous node gives rise to serious and often fatal consequences and is readily recognizable. In aged persons, the lesser frequency, the slower evolution and the greater variety of the changes, particularly of the healing or healed type, have made clinical recognition more difficult. The only recorded cases in which antemortem clinical diagnoses were made are those of Fleischner [7] and of Herscher and Bourgeois.[8] In more recent years, the use of bronchoscopic examination in the diagnosis of bronchopulmonary disease has increased enormously. The literature in this field contains several reports of the appearance of bronchial lesions caused by perforating lymph nodes (Jackson and Jackson,[9] Vinson and Toone,[10] Vinson and Pembleton,[11] Lloyd and Budetti [12] and Dighiero [13]).

Broncholithiasis is a special phase of the larger subject. Because of its peculiar symptomatology, to be noted later, it has attracted greater attention, so that reports of cases diagnosed both clinically and bronchoscopically are more numerous. This subject is reviewed by Fox and Clerf.[14]

Both Rivière (quoted by Fleischner [4]) and Brock [15] have pointed out that the bronchus of the right middle lobe is more densely surrounded by lymph nodes than are the other bronchi. This bronchus is therefore particularly vulnerable to the effects of glandular pressure and perforation, of which tuberculosis is the most frequent cause. The literature does not mention, perhaps because it is so obvious, that an added factor in the easy occlusibility of the middle lobe bronchus is its relatively small caliber.

Arnstein,[1] in the study previously mentioned, noted that perforation occurred most often on the right side and especially affected the middle lobe bronchus. Single cases of middle lobe atelectasis caused by perforating tuberculous nodes were found at necropsy by Neumann,[16] Fleischner,[4] Silverman [6] and Zdansky.[17]

Other authors described cases of middle lobe atelectasis which were studied more completely during life. Herscher and Bourgeois [8] described a case with extensive mediastinal adenopathy. When tubercle bacilli suddenly appeared in the sputum, they concluded that a node had perforated into the bronchus. Cohen and Wessler [18] described two cases with bronchoscopic findings which are reported again in this article as cases 5 and 6. In case 3 of Freedlander and Wolpaw,[19] carcinoma was suspected as the cause.

The resected right lung showed erosion of the bronchus by a tuberculous node. Dighiero [13] found two cases of middle lobe atelectasis in a series of 16 cases of bronchial tuberculosis in which no open pulmonary lesions were present. Cases of broncholithiasis of the middle lobe bronchus with resulting atelectasis also have been described. In Fleischner's [7] case, the broncholith was expectorated spontaneously. The diagnosis was made bronchoscopically in Zdansky's [17] case and by surgical exploration in the case of Anderson and Mackay.[20]

In this article, eight cases of atelectasis of the middle lobe are reported in which, during life, the cause was established as bronchial perforation by tuberculous lymph nodes.

Case Reports

Case 1. A 58 year old woman was admitted to the Beth Israel Hospital in June, 1939. About 30 years previously, she had been treated for tuberculosis for two years. She had stayed well until three months prior to admission, when she developed a cough which became progressively worse and was productive of about 120 c.c. of sputum daily. She also developed night sweats and feverishness and lost 12 pounds in weight. On admission, the temperature was 100.6° F. A rhonchus was heard in the right paravertebral region. A roentgenogram (postero-anterior view) showed infiltration of the right lower lung field. Smears of the sputum disclosed acid-fast bacilli. She was transferred to another hospital and then in November to the Montefiore Hospital. A roentgenogram showed greater density of the original shadow (figure 1*a*). A lateral view showed that this was an atelectatic middle lobe (figure 1*b*). Bronchoscopic examination showed the orifice of the middle lobe bronchus narrowed to a diameter of 2 mm. and just below this, a circular stricture of the main bronchus. Biopsy was negative. Another examination in July, 1940, showed that the middle lobe bronchus was completely occluded. The patient's condition progressively deteriorated and she died of extensive pulmonary tuberculosis in August, 1941. At necropsy the middle lobe was reduced to a firm nonaerated mass. There was an oval crater-like opening into the right main bronchus, about 2 cm. below the orifice of the upper lobe bronchus. This led directly to a caseous mass. Posteriorly the mass was continuous with the bronchial nodes and anteriorly with the narrowed middle lobe bronchus. This bronchus was followed to the hilus and was then lost in the caseous mass. Microscopic sections taken through the bronchus showed its wall to be thickened by tubercles. The middle lobe itself showed atelectasis and septal thickening with a few areas of caseation. There was extensive tuberculosis throughout the remainder of both lungs.

Case 2. A 54 year old woman was admitted to the Beth Israel Hospital in October, 1946, complaining of a progressive dry cough of three months' duration. Two years previously she had been treated at another hospital for "pneumonia." On examination, temperature was 100.2° F. Bronchial breathing and crepitant râles were heard over the right fourth and fifth interspaces anteriorly. Roentgenograms showed atelectasis of the middle lobe and slight infiltration at the apex of the left upper lobe. Bronchoscopic examination revealed narrowing of the orifice of the middle lobe bronchus by some firm tissue on the anterior wall. Biopsy showed severe inflammation, and carbon pigment was seen in one of the pieces. Smears and guinea-pig inoculation of the gastric contents showed tubercle bacilli. The patient was transferred to another hospital and from there to Sea View Hospital. The sputum contained tubercle bacilli up to April, 1947, but thereafter, cultures were

negative. Bronchoscopic examination in August, 1947, showed complete occlusion of the middle lobe orifice by scar tissue. As of September, 1948, the patient's condition was good.

Case 3. A 66 year old woman was admitted to the Beth Israel Hospital in October, 1942. Seven months previously she had developed a persistent cough, pain in the chest and weakness. Examination showed dullness and diminished breath sounds over the right lower lung anteriorly. Roentgenograms showed atelectasis of the middle lobe (figures *2a, b*). Bronchoscopic examination showed a narrowing of the orifice of the middle lobe bronchus to 3 mm. There was also a stenosis of the right lower lobe bronchus. In the region of the orifice of the middle lobe an area of black pigment under an atrophic mucosa was seen. The sputum did not contain tubercle bacilli by smear or culture. The patient has been seen regularly in the out-patient department up to December, 1948. She has a slight cough but her general condition is good. Roentgenograms show progressive shrinkage of the middle lobe shadow (figures *2c, d*). Sputum examinations have not revealed tubercle bacilli. She refuses to permit further bronchoscopic examination.

Case 4. A 70 year old woman came to the out-patient department of the Beth Israel Hospital in July, 1944, complaining of cough and slight hemoptysis of four weeks' duration. A roentgenogram showed infiltrations in the right lower lung field. Smears of the sputum did not reveal acid-fast bacilli. She was thought to have a neoplasm, for which operation was not advisable because of her age. She returned in December, 1946, complaining of intermittent hemoptysis. She had noted a wheeze in the midsternal region some time previously. Physical examination was not remarkable, except for the presence of a rhonchus over the right parasternal region. There was no change in the roentgenogram (postero-anterior view), but a lateral view showed atelectasis of the middle lobe. Bronchoscopic examination showed partial stenosis of the right upper lobe bronchus and of the main bronchus just below the middle lobe orifice. Anthracotic pigment was seen throughout the bronchial tree, including the anterior wall of the middle lobe bronchus. A biopsy from this region showed inflamed bronchial tissue with carbon pigment scattered throughout the mucosa in some sections. The patient has been seen regularly in the out-patient department up to December, 1948. She has a slight productive cough but her general condition is good. There have been no new physical or roentgenographic findings. Smears of the sputum have not revealed acid-fast bacilli.

Case 5. A 60 year old woman was first admitted to the Beth Israel Hospital in April, 1936, complaining of fever, cough and pain in the right half of the chest of two weeks' duration. On the day of admission she had noted some blood-streaked sputum. She had suffered from "bronchial asthma" for 18 years and was supposed to be sensitive to feathers. On examination she appeared acutely ill. The temperature was 104° F., and there was evidence of an acute pulmonary infection. Smears of the sputum did not show acid-fast bacilli. The temperature fell to normal in a few days. A roentgenogram (postero-anterior view) showed a dense shadow occupying the medial portion of the right lower lung field. Bronchoscopic examination showed that the mucosa of the medial and anterior walls of the main bronchus just below the orifice of the upper lobe bronchus was thickened, forming a stenosis, and several anthracotic spots studded the region. Biopsy was negative. It was thought that the patient was suffering from a neoplasm and she was given roentgen therapy, with little improvement.

After her discharge from the hospital the cough persisted, but otherwise she felt well. She was readmitted for further study in December, 1937. A roentgenogram (postero-anterior view) showed no change except for the effects of the roentgen therapy, but a lateral view showed atelectasis of the middle lobe. Bronchoscopic

examination showed that the right upper lobe bronchus was narrowed to one-half its normal caliber, and at a point 0.5 cm. below its orifice the main bronchus was stenosed in a funnel-like manner, with a reduction in caliber to about 3 mm. At this point numerous anthracotic spots studded the mucous membrane. The sputum did not contain tubercle bacilli. It has not been possible to trace this patient.

Case 6. A 64 year old woman had hoarseness and cough for four years prior to her admission to the hospital. Nine months previously she had been treated for "pneumonia" of the upper lobe of the right lung and was in bed six weeks. Cough and expectoration persisted, and she was admitted to the Montefiore Hospital in December, 1937. She stated that she had had "asthma" 12 years before but that it had gradually disappeared. She had noted its return during the previous year. On physical examination she was dyspneic on the slightest exertion. There were dullness and distant breath sounds over the right lower chest anteriorly, where a loud inspiratory rhonchus was heard. A roentgenogram showed atelectasis of the middle lobe. Examinations of the sputum failed to reveal tubercle bacilli. Bronchoscopic examination showed a thickened healed ulceration on the mesial wall of the right main bronchus, opposite the branch to the lower lobe bronchus, in the midst of which there was an area of anthracotic pigmentation. Below this the bronchus was narrowed so that the instrument could not be passed. The orifice of the middle lobe bronchus appeared completely occluded by scar tissue. Bronchographic study showed a small anterior radicle of the right main bronchus which lay in the position normally occupied by the middle lobe bronchus; there a small collection of iodized poppyseed oil was seen, and the bronchus terminated one-quarter of an inch (0.64 cm.) from its point of origin. The patient has been followed in the out-patient department since discharge. She has complained of pains in the right lower chest, cough, expectoration and occasional febrile episodes. Since 1943, she has been treated for cardiac failure. Roentgenograms have shown a shrinkage of the middle lobe shadow. Sputum examinations have not shown tubercle bacilli.

Case 7. A 67 year old woman was admitted to the Beth Israel Hospital in August, 1948, as a private patient of Dr. Gary Zucker. About eight months previously she had developed a productive cough. Subsequently, she had suffered from several febrile episodes which were diagnosed as pneumonia and were treated successfully with penicillin. She had noted a wheeze in her right chest. Examination revealed a rhonchus in the right parasternal region. Roentgenograms showed atelectasis of the middle lobe. Bronchoscopic examination showed narrowing of the right upper lobe bronchus; the orifice of the middle lobe bronchus was narrowed by a bulge, on the surface of which anthracotic pigment was seen. Biopsy showed lymphocytic infiltration of the bronchial wall; adjacent to it there was a large inflammatory mass, parts of which had the character of granulation tissue and contained many leukocytes, numerous giant cells and much anthracotic pigment. Examination of the biopsy specimen and of the sputum did not reveal acid-fast bacilli. Since discharge, she has been given a weekly injection of 300,000 units of penicillin in oil and has had no recurrence of pulmonary infection for nine months.

Case 8. A 60 year old woman was admitted to the Beth Israel Hospital in December, 1947. She had suffered from a mild "bronchitis" for 20 years. About five years previously the sputum had been blood-streaked for three days. About nine months previously the cough became worse and more productive, and six months later it also became blood-streaked and remained so. On examination there were slight dullness and diminished breath sounds in the right lower lung field anteriorly. A questionable rhonchus was heard in the right parasternal region. Roentgenograms (p-a and right anterior oblique views) showed a small area of calcification adjacent to the lower pole of the right hilus (figure 3) and the oblique also showed atelectasis of the middle lobe. Bronchoscopic examination showed a small hard mass deep

within the middle lobe bronchus. This was removed and was found to be a broncholith. Following this the patient's symptoms disappeared. She has been followed by her family physician, who reported in May, 1948, that she was well. No later roentgenograms are available.

Comment

A review of the symptomatology and clinical findings of the cases reported herein indicates a fairly typical picture. The patients were all females, ranging in age from 54 to 70 years, with all but one 60 years or over. The literature, however, does contain reports of a few cases in males. With one exception, there was no past history of pulmonary tuberculosis. The leading symptom was cough, usually slightly productive, beginning less than a year previously. Hemoptysis was present in two cases. A history of wheezing could be elicited in three cases, but it rarely was so prominent that the information was volunteered. Mild constitutional symptoms were present in the two cases with tubercle bacilli in the sputum. In three of the others, there was a history of one or more recent attacks of acute pulmonary infection, none with suppuration.

Physical examinations showed few abnormal findings. Slight alterations in the percussion note and increased breath sounds or râles in the region of the middle lobe were present in most cases. A rhonchus heard best to the right of the sternum or spine was present in many cases, particularly those in whom bronchoscopy later showed narrowing of bronchi larger than that to the middle lobe. Clubbing of the fingers was not present.

In two cases, tubercle bacilli were found in the sputum, but in the others, none was found despite many examinations. The sputa were not examined for carbon particles. In every case, roentgenograms showed atelectasis of the middle lobe (figures 1, 2, 3) without significant tuberculous or other involvement of the remainder of the lungs. Calcifications were seen at the right hilus in some (figure 3); in others, they were not seen in the conventional exposures, but were seen in overexposed (figure 2*f*) Bucky or bodysectional films. Diaphragmatic motion was normal, and there was no mediastinal swing during breathing.

Bronchoscopic examination showed a marked narrowing of the orifice of the middle lobe bronchus by a bulge or annular stricture in five cases. In four of these and in two other cases, there was involvement of the right main bronchus or one of its larger branches. In the remaining case, a broncholith was removed from the middle lobe bronchus. Anthracotic pigment was seen in the bronchial mucosa, particularly in the region of the strictures or bulges in five cases. Biopsy in one case (in which the sputum did not contain tubercle bacilli) showed a lesion suggestive of tuberculosis; in three cases, carbon pigment was seen in the microscopic sections; otherwise, there were no remarkable findings.

The subsequent course varied with the predominant type of pathologic change. One of the two patients with tubercle bacilli in the sputum de-

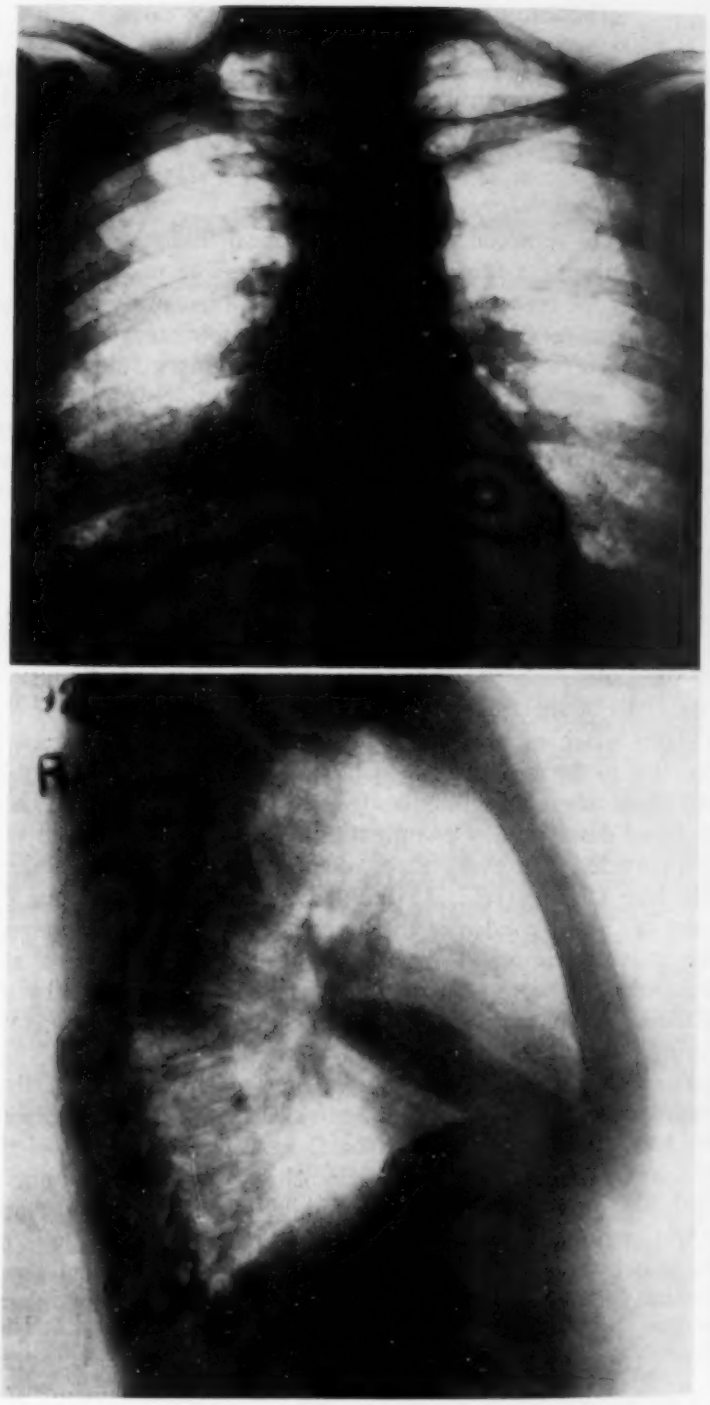
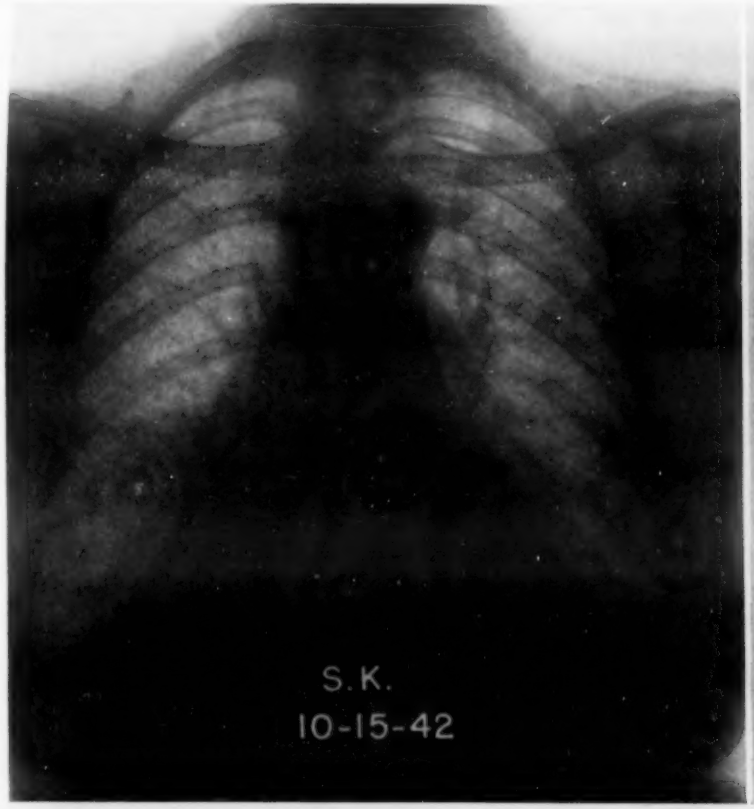


FIG. 1*a* (*above*). *Case 1.* Postero-anterior film taken September 28, 1939, shows infiltrations in the right lower lung field representing collapsed middle lobe.

FIG. 1*b* (*below*). *Case 1.* Right lateral film taken September 28, 1939, shows shadow of atelectatic middle lobe.



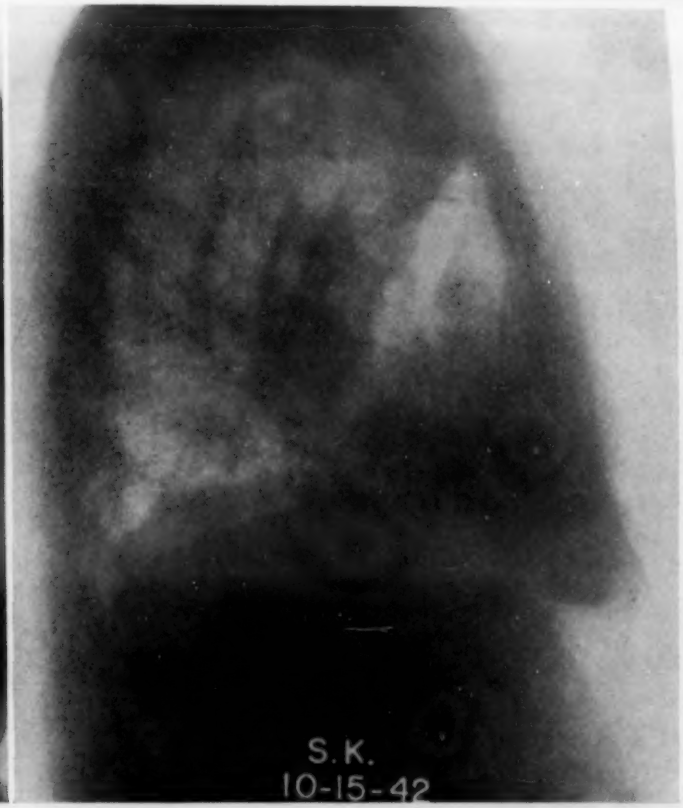


FIG. 2*a* (*left*). *Case 3.* Postero-anterior film taken October 15, 1942, shows shadow in right lower lung field representing collapsed middle lobe.

FIG. 2*b* (*right*). *Case 3.* Right lateral film taken October 15, 1942, shows shadow of atelectatic middle lobe. Streak of increased radiolucency is an artefact.

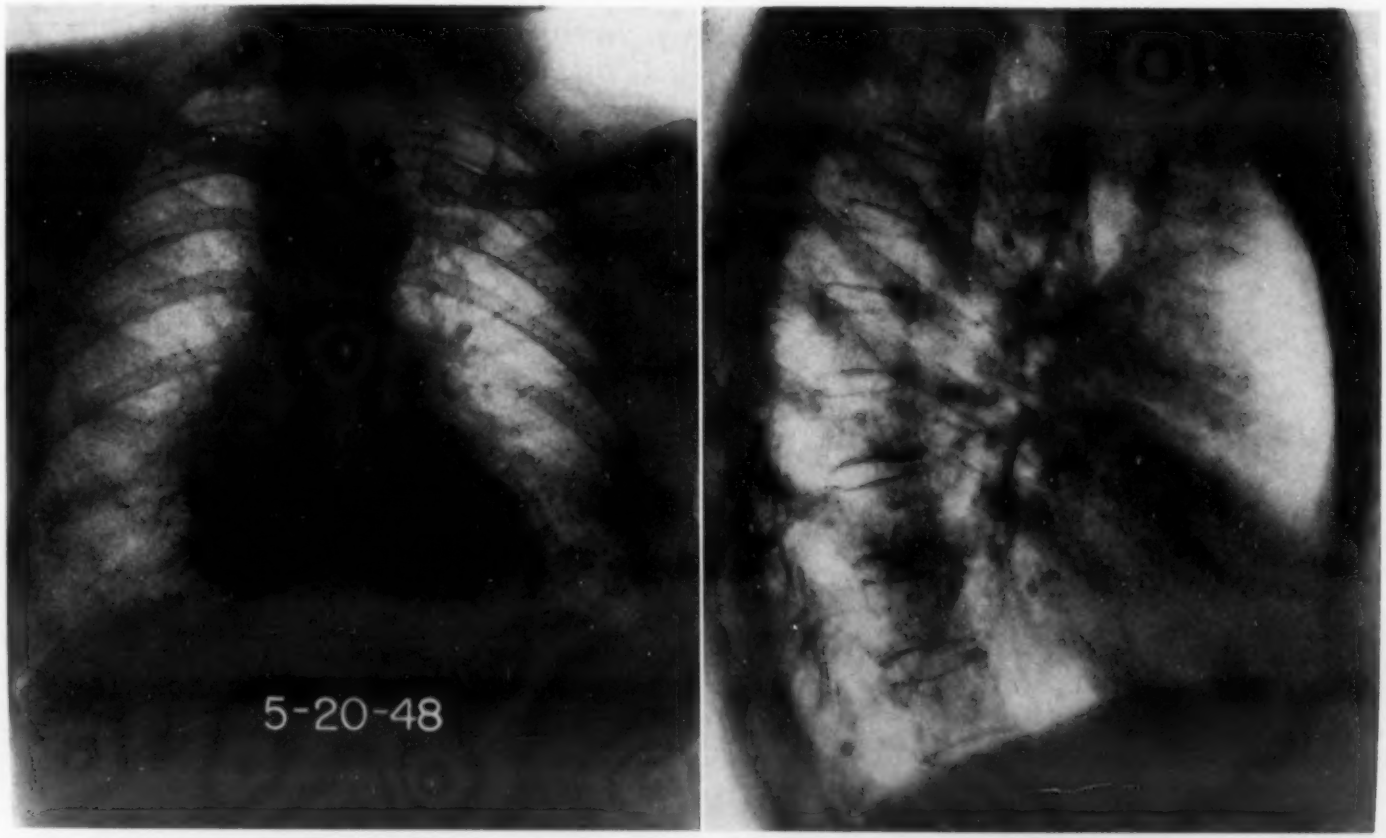
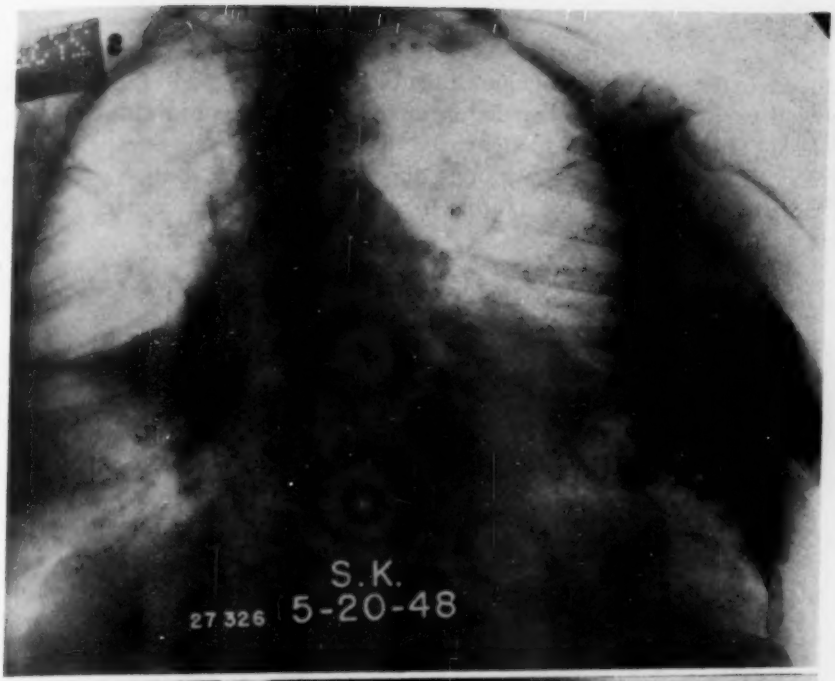


FIG. 2c (*left*). *Case 3.* Postero-anterior film taken May 20, 1948. Note the shrinkage in the shadow compared to figure 2a. No calcifications are visible at the right hilus.

FIG. 2d (*right*). *Case 3.* Right lateral film taken May 20, 1948. There has been much shrinkage in the shadow compared to figure 2b. The lower border of the middle lobe is not clearly defined.



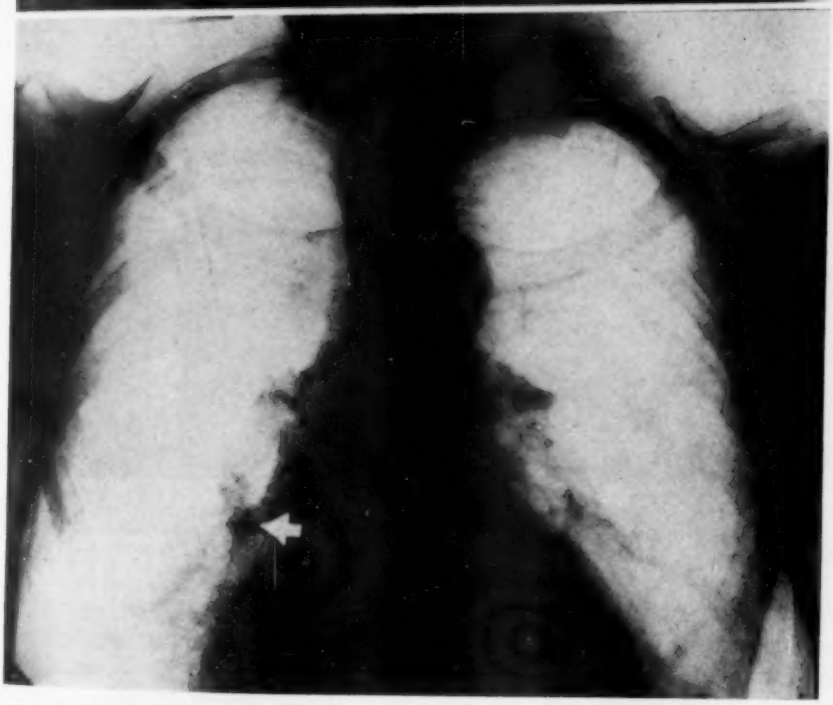


FIG. 2e (*above*). *Case 3.* Postero-anterior lordotic film taken May 20, 1948. The triangular shadow represents the collapsed middle lobe. Note how much more conspicuously the lobe is represented in this view than in figures 2*c* and *d*.

FIG. 2f (*below*). *Case 3.* Overexposed postero-anterior film taken May 20, 1948. Arrow points to calcification at right hilus; this was not visible in figure 2*c*.

veloped extensive bronchogenic spread to the lungs and died. Necropsy showed perforation and obstruction of the middle lobe bronchus by caseous nodes. The other patient improved greatly under conservative hospital care. No other pulmonary lesions appeared, and the sputum became free of tubercle bacilli after six months. She was ready for discharge from the

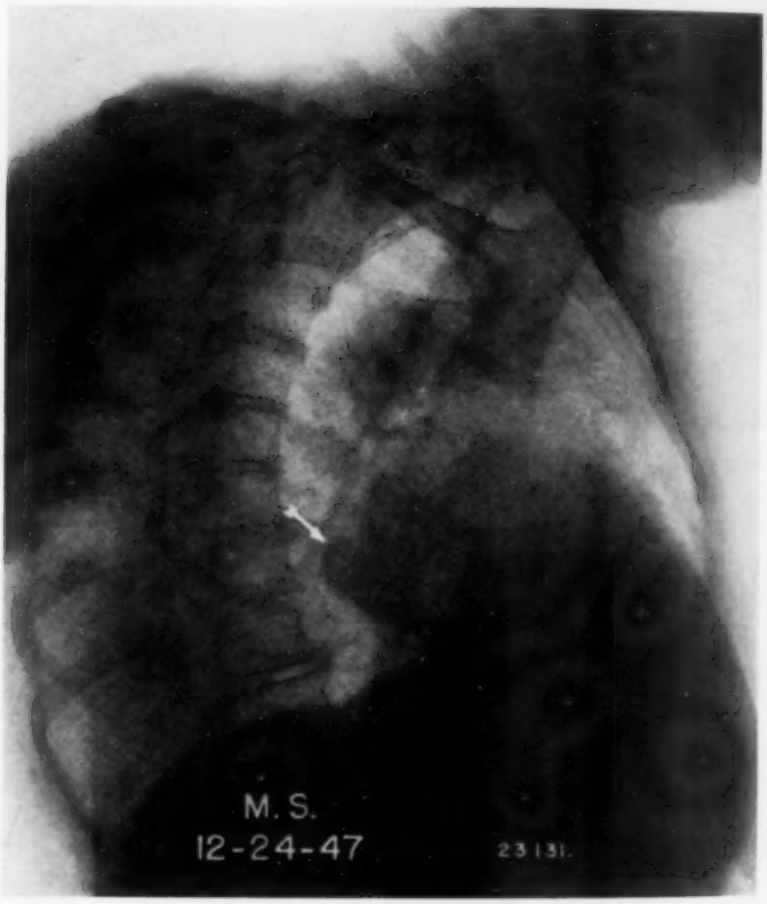


FIG. 3. *Case 8.* Right anterior oblique film taken December 24, 1947. The arrow points to a calcification representing a broncholith which was later removed from the middle lobe bronchus. A portion of the collapsed lobe can be seen distal to it.

hospital after two years. In those of the other cases that could be followed, the course has been essentially benign. Except for slight cough and expectoration, the patients are well five to 11 years after the onset. In the case of broncholithiasis, there was great improvement in symptoms after removal of the stone. In all the cases, the atelectasis of the middle lobe has persisted. There has been no suppuration in the lobe in any case.

Discussion

The accumulation of a series of this size, mostly within a few years, establishes perforation of tuberculous lymph nodes into bronchi as an outstanding cause of isolated atelectasis of the middle lobe in adults. Of course, perforations into other bronchi occur, and there are other causes of middle lobe atelectasis, but the coincidence of the two is so great as to justify its characterization as a syndrome.

In most cases, the tuberculous lymphadenitis is the result of reactivation of a dormant infection in aged persons, mostly female, in whom there is no other clinical evidence of tuberculosis. For this reason, they are first seen elsewhere than in institutions for the tuberculous. An exception is a small group of cases of tuberculosis predominantly affecting the lymphatic system, seen mostly in colored races. In these, perforation into bronchi is but an incident in the course of the generalized disease.

The clinical features which have been described are those of bronchial irritation and obstruction. They vary considerably, depending upon the site of the perforation and upon the predominant pathologic changes in the nodes and bronchus. The nodes may perforate into the middle lobe bronchus alone or may compromise it in the course of perforation into the right main bronchus. Wheezing and rhonchi are present only when branches larger than that to the middle lobe are narrowed sufficiently. The presence of tubercle bacilli in the sputum indicates a currently active tuberculous infection. The detection of carbon particles in the sputum has been described as a valuable sign of the perforation of lymph nodes which contain anthracotic pigment (Arnstein [1, 2]). Perforation of calcified bodies (broncholithiasis) often produces severe hemoptysis, and the patient also may expectorate a stone spontaneously.

The outstanding feature of the syndrome is the discovery of middle lobe atelectasis roentgenographically (Robbins and Hale [21, 22]). In a typical case, in the postero-anterior view, there is marked decrease in the size of the lobe. This assumes a pyramidal shape, with the base against the right border of the heart and the apex extending toward the lateral chest wall.[18, figure 9a] However, in most cases the borders of the shadow are ill-defined (figure 2*a*). In some, only a few infiltrations are seen (figure 1*a*). In one case a "negative" report almost would have been justifiable. Whatever the appearance of the lesion in this view, it is impossible to determine whether it is in the middle or lower lobe.

In the right lateral view, the collapsed lobe is represented by a band of increased density located in the plane of the antero-inferior portion of the longitudinal septum. The widest portion lies against the anterior chest wall or diaphragm. The upper portion of the shadow diminishes in width until it forms an apex at the junction of the longitudinal and horizontal septa (figures 1*b*, 2*b*). This view is diagnostic in most cases.

Occasionally, the shadow of the atelectatic lobe in the lateral view is

barely denser than that of normal lung, particularly if the cardiac shadow interferes (figure *2d*). In other cases, complicating pleuritis may create difficulties in interpretation. In such instances, the postero-anterior lordotic view is of great value. In this view, the atelectatic lobe is represented by a triangular shadow, with its base on the right cardiac border below the hilus and its apex somewhere in the middle of the lower lung field (figure *2e*). The upper and lower margins are sharp (Fleischner,[23] Doig,[24] Rigler [25]).

We have recently made postero-anterior laminagrams in several of the cases. The typical shadows appear in certain sections with much greater clarity than in the conventional view. In lateral laminagrams, no distinctive shadows are seen. In one case, an accidental pneumothorax also resulted in accentuation of the middle lobe shadow. In two of the cases that were followed, there began at about the fourth year a progressive shrinkage in the size of the shadows. As a result, the shadow disappeared almost completely in the postero-anterior view and diminished greatly in width in the lateral view (figures *2a, b, c, d*).

When the diagnosis of middle lobe atelectasis has been made roentgenographically, speculation as to the cause naturally is aroused. Several findings which, when present, are important clues to a tuberculous etiology are: (1) calcifications at the right hilus; (2) the presence or, especially, the sudden appearance of tubercle bacilli in the sputum in the absence of open pulmonary lesions; (3) the presence of carbon particles in the sputum; and (4) the expectoration of broncholiths.

Ultimately, the diagnosis is established bronchoscopically. Reference already has been made to the main diagnostic features; further details can be obtained from the literature. Specific tuberculous lesions, such as ulcers, granulation tissue or protruding nodes, though not seen in this series, have been reported by others. Their presence, whether seen grossly or in histologic sections, is diagnostic. In the absence of such lesions, we have considered the presence of anthracotic pigment in the bronchial mucosa, particularly in the region of strictures, as circumstantial evidence of lymph node perforation. The quoted necropsy studies of Fleischner,[4] Arnstein [1] and Rich [3] furnish strong support for this viewpoint.

We have seen several cases of middle lobe atelectasis (not included here) in which endoscopy showed a bronchial stricture, but without anthracotic pigment. It is impossible to know, pending ultimate histologic studies, whether these strictures are always tuberculous in origin, or are sometimes secondary to other types of infection. Also, in a few cases with typical roentgenographic changes, no gross endobronchial lesions are demonstrable. In these cases, there is an obliterative bronchitis of the larger branches of the middle lobe bronchus secondary to an unidentified infection (case 4 of Freedlander and Wolpaw [19]).

No attempt has been made to compile data on the incidence of isolated middle lobe atelectasis in other conditions which usually cause bronchial

obstruction. It is comparatively uncommon in bronchogenic carcinoma, a condition in which atelectasis of other lobes is found so frequently. It has been reported in a few cases of bronchial invasion or compression by nodes involved by metastatic neoplasm, lymphoblastoma and sarcoidosis. It also has been noted in a few cases of benign adenoma and of foreign body in the bronchus. This leads to the conclusion that bronchial perforation by tuberculous nodes is by far the leading cause of middle lobe atelectasis and should be suspected above all other conditions. This is of special importance in view of the current emphasis on the early diagnosis of carcinoma. It is noteworthy that in several of the cases in this series, as well as in the literature, carcinoma was the first diagnosis made and treatment was given accordingly. In future cases, cytologic examination of the sputum for cancer cells should be valuable in this sphere.

This series is not sufficiently large to justify authoritative statements regarding treatment. Cases which show evidence of active tuberculous infection bacteriologically or histologically should be given institutional care. This should be supplemented by more specific measures, such as administration of streptomycin and local endoscopic treatment. The two cases in this series were seen prior to the availability of this drug. The prognosis in the group without tubercle bacilli in the sputum is amazingly good. Attempts at dilatation of the strictures are futile. The mild symptoms are controlled easily by medication. Weekly injections of penicillin in oil may be of value in preventing recurrences of infection in the collapsed lobe. Unless suppuration should appear, which thus far has not occurred in any of the cases in this series, there should not be undue haste to perform resection, particularly in aged patients.

Summary

1. In aged white persons, reactivation of a quiescent tuberculous mediastinal lymphadenitis may result in gradual perforation of the nodes into large bronchi.

2. In most instances the process is relatively benign, so that healing, with stricture formation, has already occurred by the time the patients are first seen. Occasionally progressive bronchial and, later, pulmonary tuberculosis develops.

3. The bronchus of the right middle lobe is particularly vulnerable to this process because of its position in relationship to chains of nodes and because of its small caliber. Atelectasis of the lobe results.

4. Eight cases of atelectasis of the middle lobe secondary to perforation of lymph nodes into bronchi are reported. All were diagnosed during life. All were in female patients (a few in males are reported in the literature), and with one exception, they were all 60 years of age or over.

5. The patients were not under treatment for tuberculosis when seen for the first time in a general hospital.

6. The chief symptoms—cough, expectoration and sometimes wheezing

—are those of bronchial irritation and obstruction. These symptoms usually are not severe. If perforation by a calcified spicule (broncholithiasis) occurs, hemoptysis may be profuse.

7. In two cases, tubercle bacilli were found in the sputum, indicating an active infection. One patient died and the other recovered.

8. In the other six cases, no evidence of active infection appeared. Some patients are alive and relatively well as long as 11 years after the diagnosis was made.

9. The roentgenographic features of middle lobe atelectasis are described. The inadequacy of the postero-anterior view, the greater value of the lateral view, and the usefulness of the postero-anterior lordotic view are emphasized. The potential value of laminagraphy is noted.

10. In such cases, calcifications at the hilus of the right lung are highly suggestive of a tuberculous etiology. These shadows, when obscure in conventional exposures, often may be demonstrated by special methods.

11. A tuberculous etiology also is indicated by the presence of tubercle bacilli in the sputum or the expectoration of broncholiths.

12. Bronchoscopic examination may reveal specific tuberculous lesions such as ulcers, granulation tissue or protruding nodes. Most often, however, there is found a marked narrowing of the orifice of the middle lobe bronchus by scar tissue, forming a stricture or bulge. The presence of anthracotic pigment in the vicinity of the scar is regarded as evidence of previous lymph node perforation.

13. The other important bronchial diseases, particularly carcinoma, cause isolated middle lobe atelectasis much less frequently than does perforation by tuberculous lymph nodes; therefore, this condition should be suspected above all others.

14. The treatment, in cases with active infection, should be institutional care supplemented by specific measures.

15. Treatment, in cases with healed strictures, should be symptomatic and conservative unless suppuration or severe hemorrhage occurs.

Addendum

The following pertinent articles have appeared since the submission of this article:

1. Brock, R. C.: Post-tuberculous broncho-stenosis and bronchiectasis of the middle lobe, Thorax **5**: 5, 1950.

2. Rubin, E. H., and Rubin, M.: The shrunken right middle lobe. Dis. Chest **18**: 127, 1950.

3. Clinico-pathologic conference in Am. J. Med. **10**: 393, 1951.

Acknowledgments

The author wishes to express his appreciation to Dr. M. L. Som and Dr. L. M. Arnold, who performed the bronchoscopic examinations, to Dr. A. J. Bendick and staff, for cooperation in the roentgenographic studies, and to Dr. H. Wessler, for valuable advice and criticism. He is indebted to Dr. G. Zucker for permission to report case 7, and to Sea View Hospital

for follow-up data on case 2. Case 6 and the latter phase of case 1 were observed by the author on the Division of Pulmonary Diseases of the Montefiore Hospital for Chronic Diseases during the directorship of Dr. H. Wessler and the late Dr. M. Pinner.

BIBLIOGRAPHY

1. Arnstein, A.: Indurative und Zerfallsvorgänge in den mediastinalen Lymphknoten im höheren Alter mit Schädigung der benachbarten Organe, Beitr. z. Klin. Tuberk. **85**: 197 and 343, 1934.
2. Arnstein, A.: Non-industrial pneumoconiosis, pneumoconio-tuberculosis and tuberculosis of the mediastinal and bronchial lymph glands in old people, Tubercule **22**: 281, 1941.
3. Rich, A. R.: The pathogenesis of tuberculosis, 1944, C. C. Thomas, Springfield, Ill.
4. Fleischner, F.: Die tuberkulöse Bronchostenöse und ihre Unterscheidung vom Bronchuscarcinom, Beitr. z. Klin. Tuberk. **87**: 553, 1936.
5. Auerbach, O.: Perforation of tuberculous lymph nodes into the trachea and bronchi, Arch. Otolaryng. **39**: 527, 1944.
6. Silverman, G.: Tuberculosis of the trachea and major bronchi, Dis. Chest **11**: 1, 1945.
7. Fleischner, F.: Atelektase und atelektatische Pneumonie bei Austossung oder Durchbruch eines tuberkulösen Drüsenherdes in den Bronchus, Beitr. z. Klin. Tuberk. **86**: 72, 1935.
8. Herscher, M., and Bourgeois, P.: Adénopathie mediastinale tuberculeuse de l'adulte et "complexe gangliopulmonaire secondaire." Aspect de lobite moyenne droite, Bull. et mém. Soc. méd. d. hôp. de Paris **53**: 44, 1937.
9. Jackson, C., and Jackson, C. L.: Bronchoscopy, esophagoscopy and gastroscopy, 1937, W. B. Saunders Co., Philadelphia, p. 322.
10. Vinson, P. P., and Toone, E. C.: Pulmonary symptoms resulting from ulceration of hilar nodes into a bronchus, West Virginia M. J. **33**: 200, 1937.
11. Vinson, P. P., and Pembleton, W. E.: Ulceration of tuberculous hilar lymph node into lumen of bronchus, with bronchoscopic removal, Ann. Otol., Rhin. and Laryng. **49**: 797, 1940.
12. Lloyd, M. S., and Budetti, J. A.: Bronchoscopy in pulmonary tuberculosis, J. Thoracic Surg. **12**: 611, 1943.
13. Dighiero, J. C.: Traqueobronquites Tuberculosas Clinicamente Primitivas o Puras, Hoja tisiol. **5**: 203, 1945.
14. Fox, J. R., and Clerf, L. H.: Broncholithiasis, Ann. Int. Med. **23**: 955, 1945.
15. Brock, R. C.: Observations on the anatomy of the bronchial tree with special reference to the surgery of lung abscess. Part III. The middle lobe, Guy's Hosp. Rep. **92**: 82, 1943.
16. Neumann, W.: Die Klinik des Lungenkrebses, Jahresk. f. ärtzl. Fortbild. **24**: 1, 1933.
17. Zdansky, E.: Der Mittellappen als Punctum minoris resistentiae der Lunge, Wien. klin. Wchnschr. **58**: 197, 1946.
18. Cohen, A. G., and Wessler, H.: Clinical recognition of tuberculosis of the major bronchi, Arch. Int. Med. **63**: 1132, 1939.
19. Freedlander, S. O., and Wolpaw, S. E.: Chronic inflammatory lesions of the lung simulating bronchiogenic carcinoma, J. Thoracic Surg. **9**: 530, 1940.
20. Anderson, W. S., and Mackay, J. B.: Broncholithiasis, Dis. Chest **10**: 427, 1944.
21. Robbins, L. L., and Hale, C. H.: The roentgen appearance of lobar and segmental collapse of the lung. A preliminary report, Radiology **44**: 107, 1945.
22. Robbins, L. L., and Hale, C. H.: The roentgen appearance of lobar and segmental collapse of the lung. V. Collapse of the right middle lobe, Radiology **45**: 260, 1945.
23. Fleischner, F.: Das Röntgenbild der interlobären Pleuritis und seine Differentialdiagnose, Ergebn. d. med. Strahlenforsch. **2**: 199, 1926.
24. Doig, A. T.: Atelectatic bronchiectasis of the right middle lobe, Tubercle **27**: 173, 1946.
25. Rigler, L. G.: The chest, 1946, The Year Book Publishers, Chicago, Ill.

HYPERCHOLESTEREMIA: AN ANALYSIS OF 529 CASES AND TREATMENT OF 297 BY A LOW ANIMAL FAT DIET AND DESICCATED THYROID SUBSTANCE *

By W. W. PRIDDLE, M.D., F.A.C.P., *Toronto, Canada*

EVIDENCE is gradually accumulating that the genesis of human atherosclerosis is somehow associated with cholesterol metabolism. Myxedema, poorly-controlled diabetes, xanthomatosis and nephrosis have in common a high serum cholesterol, and they are prone to develop premature and severe grades of atherosclerosis.

Anitschkow [1] in 1912, by feeding rabbits pure cholesterol dissolved in a vegetable oil, was successful in producing experimental atherosclerosis. In 1933 he expressed the opinion, in reviewing the literature up to that time, that the experimental lesions in rabbits were the same as those of human atherosclerosis. Duff [2] stated in 1935, in an extensive review, that there was insufficient evidence on which to assume that a disturbance of cholesterol or lipoid metabolism had any part in the etiology of human arteriosclerosis. Following this Leary,[3, 4] who had previously published arguments in favor of considering human atherosclerosis as a disturbance of cholesterol metabolism, reaffirmed his stand. He added that stress appeared to be responsible for the localization of the lesion, and that thyroid disturbances had some relationship to the deposit of cholesterol in the intima. He advocated the restriction of cholesterol in the diet as a prophylactic measure against atherosclerosis.

In 1936 Steiner and Kendall [5] reported the successful production in dogs, by feeding cholesterol plus thiouracil, of arterial lesions closely resembling human atherosclerosis in both distribution and morphology. In rabbits, Turner [6] demonstrated that the giving of whole thyroid substance simultaneously with cholesterol feedings prevented hypercholesteremia and atherosclerosis. Thyroxin was not nearly so effective as whole thyroid substance. Again in rabbit experiments, thyroidectomy resulted in a slight increase in serum cholesterol on a normal diet, but the level was markedly increased in the presence of cholesterol feedings. A single injection of thyroxin was followed by a significant drop in the level of blood cholesterol in rabbits having induced hypercholesteremia.

Fleischmann and Shumacker [8] have presented experimental evidence to show that, with the administration of thyroxin to thyroidectomized rabbits and rats, the change in the serum cholesterol level is due to alteration in distribution between the plasma and tissue fractions and not to any change in the total body cholesterol. Fleischmann and Fried [9] showed that the

* Received for publication March 24, 1951.

hypercholesteremia induced in chicks by the administration of estrogens could be prevented by thyroxin and likewise that there was no change in the total body cholesterol. Horlick and Katz [10] implanted stilbestrol pellets in chickens and recorded somewhat higher blood lipid and cholesterol levels on a normal diet than on a low fat diet. However, hypercholesteremia and atherosclerosis were produced in a large proportion of chickens on both types of diet. In a control group on a low fat diet there was no spontaneous atherosclerosis, although it occurred in 40 per cent of the chickens on a normal diet. Serum cholesterol levels were slightly higher in the control group on a low fat diet than on a normal diet.

Bloch and Rittenberg,[20] using isotope technic, demonstrated in rats that cholesterol can be formed in the body from acetates. Thus, any fat, and conceivably other dietary components, could act as a source for the synthesis of excessive amounts of cholesterol in a subject with a disturbed metabolism.

In the clinical field, numerous investigators have reported an elevated serum cholesterol in patients with coronary arteriosclerosis. Davis, Stern and Lesnick,[11] Steiner and Domanski [12] and Lerman and White [13] all recorded a distinctly elevated serum cholesterol, as compared to controls, in cases of coronary arteriosclerosis. Boas, Parets and Adlersberg [14] reported an elevated serum cholesterol in 58 per cent of patients in whom coronary arteriosclerosis began under the age of 50, and similar changes were noted in the families of these individuals. Morrison, Hall and Chaney [15] observed that coronary thrombosis appeared at an earlier age in patients with an elevated serum cholesterol. Underdahl and Smith [16] found hyperlipemia in eight of 14 women under 40 years of age with coronary artery disease.

Turner and Steiner [17] demonstrated in a group of normal individuals that the serum cholesterol level remained remarkably constant over a period of one year. Davis, Stern and Lesnick [11] confirmed this finding over a three year period, and they also noted no difference in the serum cholesterol level in the various age groups. Page et al.[18] found the same values in older individuals as in young adults. However, Chaplin [19] recorded good evidence that the clinical conditions in which hypercholesteremia occur are more prevalent in the older age groups. Steiner and Domanski [12] called attention to the wide fluctuation of the serum cholesterol levels in patients with coronary arteriosclerosis.

Many excellent reviews of the published work on arteriosclerosis have recently appeared in the literature. Reference is made to papers by Katz and Dauber,[21] Gubner and Ungerleider,[22] Steiner,[23] and the combined Staff Clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York, on cholesterol metabolism and arteriosclerosis.[24]

Steiner [24] used a low cholesterol diet in 10 patients who had had coronary thrombosis. He observed them for from four to 14 months. He reported lower serum cholesterol levels as compared to the control period in five cases.

There was also less fluctuation of the level of serum cholesterol while on the low cholesterol diet. In four patients with coronary arteriosclerosis, he estimated the amount of sterol in the stool while they were on a high and then a low fat and low cholesterol diet for six weeks. No difference was recorded. As there was only a very slight increase in the serum cholesterol levels on high fat and high cholesterol feedings, it was considered that the cholesterol was absorbed and either metabolized or deposited in the tissues.

Although there are large gaps in our knowledge of atherosclerosis, it would appear that real progress has been made. The literature contains considerable evidence that cholesterol or some closely allied substance has a prominent place in the genesis of atherosclerosis. There would seem to be good reason, in the present state of our knowledge, to limit the intake of animal fat in the diet of individuals in whom we suspect a disturbed cholesterol metabolism.

Turner and Steiner [17] gave desiccated thyroid substance for six weeks in doses of 0.5 to 4 gr. to 10 patients with various diseases, five of whom probably had arteriosclerosis. Four cases had hypercholesteremia. In all patients there was a sharp drop in the level of serum cholesterol, accompanied by a rise in basal metabolic rate averaging 20 per cent. The control estimations of the basal metabolic rate ranged from plus 8 to minus 10. They noted that a rise in serum cholesterol levels followed when thyroid medication was discontinued. Lerman and White,[18] working with patients under 40 years of age with coronary heart disease, found a low basal metabolic rate in one-half of their cases. In 22 of 28 patients the serum cholesterol was over 250 mg. per 100 c.c. The serum cholesterol was lower and the basal metabolic rate higher on thyroid medication. They also reported that in all but two cases on thyroid therapy the anginal pain diminished or disappeared. Davis, Stern and Lesnick [11] did not find any significant depression of the basal metabolic rate in patients with hypercholesteremia and coronary arteriosclerosis as compared to the control group.

There would seem to be experimental and clinical evidence that hypothyroid states favor the development of hypercholesteremia and atherosclerosis. It was considered that it might be of value, particularly in the presence of any degree of hypothyroidism, to administer appropriate doses of desiccated thyroid substance in cases with elevated serum cholesterol levels, to prevent or retard the development of atherosclerosis.

Method and Material

Estimations of serum cholesterol on patients seen in an office consultant practice limited to internal medicine were started in April, 1946. Although the study was continued, only the findings to October, 1949, were utilized for this report. The group numbered 1,089 patients. Because of a special interest in hypertension, more than an average percentage of such cases were included. Each patient had a complete examination, including ophthalmo-

scopic study, blood sugar, basal metabolic rate, electrocardiogram and fluoroscopic study of the heart and the arch of the aorta. The serum cholesterol was estimated by the Reinhold and Shiels modification of the Myers and Wardell method. All determinations were performed in the same laboratory by the same personnel. Levels above 250 mg. per 100 c.c. were considered abnormally high. Our laboratory informed us in April, 1949, that anhydrous sodium sulfate was replacing plaster of Paris as a drying agent in the estimation of serum cholesterol. As a result of this, the levels were found to be approximately 25 mg. higher than previously. According to the new method, 275 mg. per 100 c.c. was considered the high normal limit. For the purpose of this study, corrections were made by deducting 25 mg. from all estimations after April, 1949.

Of the 529 patients with elevated serum cholesterol, 297 were available for treatment. Thirty-four were treated with desiccated thyroid substance and 49 with diet low in animal fat. The remaining 214 patients were treated with both a low animal-fat diet and desiccated thyroid substance. A diet low in animal fat restricted the intake of egg yolk, whole milk, cream, butter, cheese, ice cream, meat fat, including fried food, gravy and lard. The daily dose of desiccated thyroid substance varied from 0.5 to 2 gr., with an occasional patient receiving 3 gr. Serum cholesterol levels were estimated at three-month intervals during the period of the investigation.

Results

Estimations of the basal metabolic rate were accepted as satisfactory on 243 patients. The range of the basal metabolic rate was from minus 38 to plus 25, with an average for the group of 99.75 per cent. Only 65 cases had a basal metabolic rate of minus 10 or less.

Cases were grouped in figure 1 according to the range of serum cholesterol. Of 1,089 cases, 529 (or 48.6 per cent) showed serum cholesterol estimations above 250 mg. per 100 c.c. Two hundred sixty-seven (or 50.5 per cent) of those with elevated serum cholesterol had levels over 300 mg. per 100 c.c.

In figure 2 the distribution of cases with elevated serum cholesterol was arranged by age groups. Seven hundred sixty-eight (or 70.5 per cent) of the series were over 40 years of age. Fifty-nine per cent of these had an elevated serum cholesterol.

The data in the two preceding figures were combined in table 1 to present a more comprehensive picture of the number of cases in each age group and their distribution in the various ranges of serum cholesterol. There was a consistent increase in hypercholesteremia with advancing age.

The number and percentage of cases with an elevated serum cholesterol in the various clinical conditions encountered were recorded in table 2. Cases might have two or more diagnoses, such as hypertension, arteriosclerosis and obesity. In establishing criteria of retinal arteriosclerosis

TABLE I

The Distribution of 1,089 Cases According to Age Group and Range of Serum Cholesterol

Age Group	Range of Serum Cholesterol							
	Under 99	100–149	150–199	200–249	250–299	300–349	350–399	400 and over
Under 20		1	10	4	1			
20–29		5	35	34	8		1	
30–39		10	64	82	38	27	4	1
40–49	1	10	36	105	63	54	15	4
50–59		4	23	54	76	56	19	17
60–69		5	17	37	55	30	22	11
70–		2	7	13	11	8	5	4

for purposes of this investigation, certain difficulties were encountered. This was particularly true of the hypertensive group. Either diffuse arteriosclerosis or atheroma of the larger arteries could account for the compression of the veins by the arteries or localized caliber variations frequently observed. It was decided to include those cases showing instances of sharp nicking of the veins by the larger arteries. Coronary arteriosclerosis in-

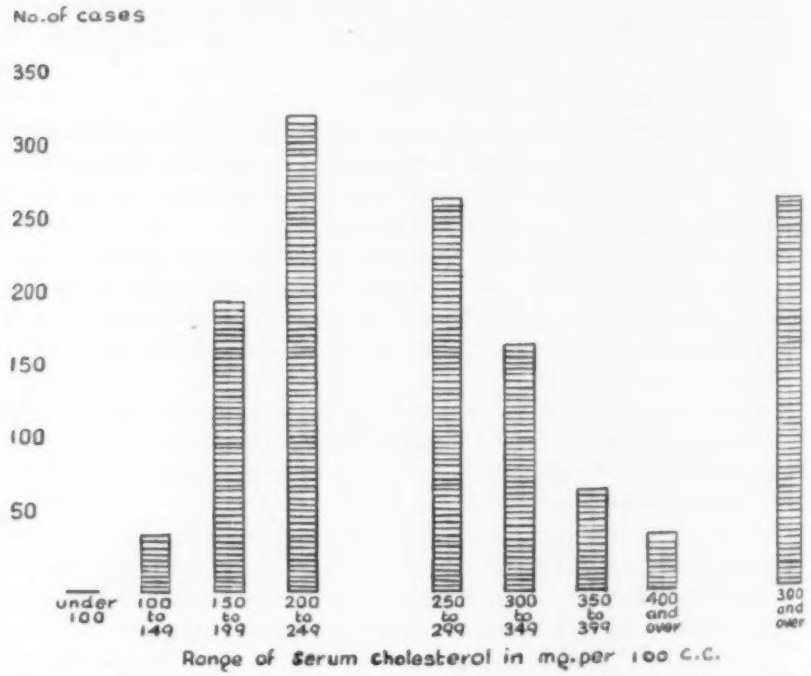


FIG. 1. The range of serum cholesterol in 1,089 cases. Five hundred twenty-nine (or 48.6 per cent) showed serum cholesterol estimations above 250 mg. per 100 c.c. Two hundred sixty-seven (or 50.5 per cent) of those with elevated serum cholesterol had levels over 300 mg. per 100 c.c.

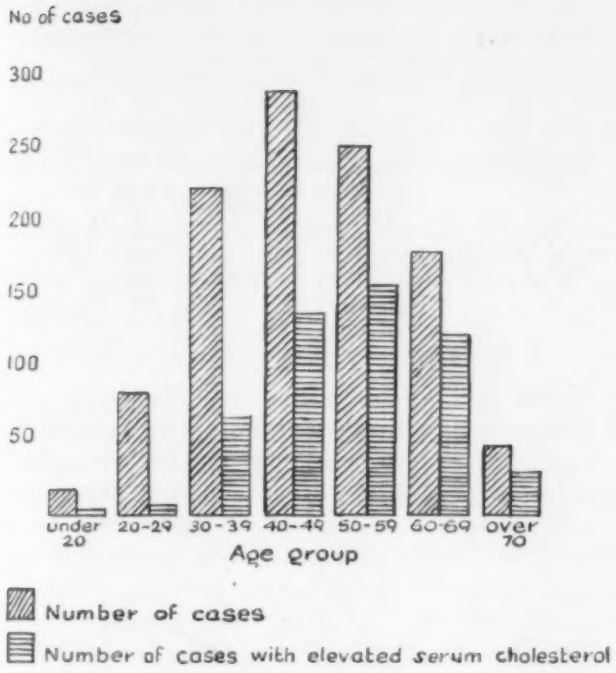


FIG. 2. Arrangement in age groups of 1,089 cases studied and 529 with elevated serum cholesterol. The comparative number of cases with hypercholesteremia consistently increased with advancing age.

cluded only cases who had had myocardial infarction or angina of effort with electrocardiographic confirmation. A cerebral vascular accident, exclusive of embolism or rupture of an aneurysm of the circle of Willis, was required for a diagnosis of cerebral arteriosclerosis. Good evidence of the presence of obliterative vascular disease of the arteries of the lower ex-

TABLE II

The Number of Cases and Percentage of Cases with Elevated Serum Cholesterol in Various Clinical Conditions Encountered

Clinical Diagnosis	Total Number of Cases	Number of Cases with Elevated Serum Cholesterol	Percentage of Cases with Elevated Serum Cholesterol
Arteriosclerosis	160	116	72.5
Retinal vessels	90	66	68.7
Coronary vessels	86	60	69.7
Cerebral vessels	31	11	35.4
Peripheral vessels	9	5	55.5
Associated Diseases			
Hypertension	326	215	65.9
Obesity	121	53	43.8
Diabetes mellitus	32	22	68.7
Cholelithiasis	17	10	58.8

TABLE III

Results of Treatment with Low Animal Fat and Desiccated Thyroid Substance on the Average Serum Cholesterol Level

Treatment Period in Months.....	0	6	12	18	24	30	36
Number of Cases Treated	Average Serum Cholesterol Level mg./100 c.c.						
55	259	267	271		259		251
145			278	275	279		264
205					285	277	277
214						287	279

tremities was present in all cases included under peripheral arteriosclerosis. The results of fluoroscopic study of the arch of the aorta were not sufficiently definite to warrant acceptance of the findings as the sole basis for a diagnosis of arteriosclerosis. Serum cholesterol levels were elevated in 72.5 per cent of cases with arteriosclerosis. Coronary arteriosclerosis showed 69.7 per cent with hypercholesteremia. Similar figures were recorded for retinal arteriosclerosis, hypertension and diabetes mellitus. Obesity showed a lower incidence (43.8 per cent) than one would have expected from previous work. This may have been due to the fact that cases with mild and moderate clinical obesity were included and represent a substantial percentage of the group.

There has been ample evidence of the relationship of diabetes mellitus and hypothyroidism to hypercholesteremia and atherosclerosis. The part played by sex hormones, emotional disturbances and alcohol has not been clarified. In some patients it appeared that these factors were influencing cholesterol metabolism. However, statistical analysis of our group failed to produce clear-cut confirmation of this impression, and it was considered inadvisable to include the data in this communication.

Tables 3, 4 and 5 recorded, at intervals during treatment, the average serum cholesterol level of groups treated from six months to two years by

TABLE IV

Results of Treatment with Low Animal Fat Diet on the Average Serum Cholesterol Level

Treatment Period in Months.....	0	6	12	18	24	30	36
Number of Cases Treated	Average Serum Cholesterol Level mg./100 c.c.						
1	267	250	285		250		250
24			267	242	261		256
46					284	257	262
49						274	213

the various methods employed. With the exception of the five cases treated for three years with desiccated thyroid substance alone, all groups showed a lower average serum cholesterol level at the end of treatment than at the beginning. However, the improvement was not marked or consistent.

The effect of treatment on the serum cholesterol level of individual cases was summarized in table 6. Although 46 per cent of patients showed improvement, a large number continued to have periods of hypercholesteremia and showed the characteristic wide swing of serum cholesterol level. Owing to this marked fluctuation in patients with hypercholesteremia, it was apparent that three months was too long an interval for accurate recording of results of treatment. The series treated by desiccated thyroid substance and a low animal fat diet separately were too small for accurate comparisons with the larger group, in which a low animal fat diet was combined with desiccated thyroid substance. However, it was interesting to note that improvement was recorded in 55 per cent of cases treated by low animal fat diet alone, whereas approximately 45 per cent were improved in each of the other series.

TABLE V

Results of Treatment with Desiccated Thyroid Substance on the Average Serum Cholesterol

Treatment Period in Months	0	6	12	18	24	30	36
Number of Cases Treated	Average Serum Cholesterol Level mg./100 c.c.						
5	253	264	220		195		268
13			247	240	226		231
31					264	254	237
34						268	256

TABLE VI

Analysis of the Effect on the Serum Cholesterol Level of Individual Cases with the Various Methods of Treatment Employed

Serum Cholesterol Level	Method of Treatment		
	Low Animal Fat Diet and Desiccated Thyroid	Low Animal Fat Diet	Desiccated Thyroid
Lowered	95	27	15
Unchanged	102	21	15
Elevated	17	1	4

In table 3 it was noted that the initial average serum cholesterol level was higher with each succeeding group. This was less marked in tables

4 and 5. In our search for an explanation, the initial serum cholesterol levels of the 1,089 cases studied were grouped according to year and averaged. The results, recorded in table 7, showed that the average initial serum cholesterol level of all cases was approximately the same for each year. Thus the progressively higher initial serum cholesterol level applied only to those cases with elevated serum cholesterol and presumably abnormal cholesterol metabolism.

TABLE VII

The Average Serum Cholesterol Level of 1,089 Cases Arranged According to Year

Year	Average Serum Cholesterol
1946	244
1947	237
1948	234
1949	236

As the study progressed, patients complained about loss of weight and restriction of fat in their diet. They were then encouraged to take more vegetable fats, such as vegetable shortening, peanut butter, vegetable oils and margarine. Margarine first became available on the Canadian market 10 months before the termination of this investigation. However, an analysis of individual cases showed only 33 instances in which there was a distinct and sustained rise of the serum cholesterol level during this 10 month period.

DISCUSSION

Katz and Dauber [21] have pointed out that "the serum cholesterol reflects a balance between the rate at which cholesterol enters the blood from depots, from sites of synthesis or exogenous sources, and that at which it leaves the blood to be excreted, destroyed or stored."

Any dietary régime in ambulatory patients is notably difficult to apply accurately. Vegetable fats have been unrestricted in the diet in this study. Although phytosterols are not absorbed by the intestinal mucosa, hyperlipemia from fatty acids could result. This would necessitate an adequate supply of cholesterol for esterification, which most probably would be supplied by synthesis from acetates.

The patients were encouraged to take extra carbohydrates and proteins to maintain an adequate caloric intake. This should have spared the fat depots and prevented an extra demand on cholesterol for the transport of fatty acids. A maintenance dose of mixed vitamins was prescribed, but large doses of vitamin B complex were not used. Thus the oxytropic action of riboflavin, niacin and thiamine and the lipotropic effect of choline, inositol and pyridoxine were not taken into consideration in this study.

Anderson [28] suggested that other lipoid substances, such as phospholipids, less easily estimated, might play as important a part as cholesterol

in transport of fatty acid. Furthermore, Leary [26] stated that the lesions of atherosclerosis were due to the deposit in the subendothelial layer of the arterial intima of cholesterol esters, rather than of free cholesterol.

The evidence of the relationship of the metabolism of cholesterol, and possibly other lipoid substances, to atherosclerosis is too strong to be ignored. With the above points in mind, this study is to be continued. A diet restricting vegetable as well as animal fats is now being prescribed for the series reported in this paper. Another group of patients with elevated serum cholesterol is being followed without any treatment by diet or desiccated thyroid substance. Owing to the wide fluctuation in serum cholesterol levels in many patients with hypercholesteremia, repeated estimations at frequent intervals are necessary.

Since the work of compiling this paper was begun, two important contributions to the subject have appeared in the literature. Stark,[27] using a rice diet containing not more than 5 gm. of fat in 125 patients with hypertensive vascular disease, has recorded a substantial reduction in hypercholesteremia in 98.4 per cent of cases. Gofman [28] has demonstrated, by using an analytic ultracentrifuge, a class of lipid and lipoprotein molecules in the serum of man and cholesterol fed rabbits, associated with atherosclerosis. Partial dietary restriction of fat and cholesterol was accompanied by a gradual reduction in the serum level of such molecules. Although there was a general trend toward a higher concentration of these molecules with higher serum cholesterol levels, the serum cholesterol estimation was of no value in predicting the concentration of these atypical molecules.

Summary

Evidence of the relationship of cholesterol metabolism to the development of atherosclerosis has been reviewed.

In a series of 1,089 patients studied, the serum cholesterol was over 250 mg. per 100 c.c. in 529, or 48.6 per cent of the cases. The level was over 300 mg. per 100 c.c. in 50.5 per cent of the group with elevated serum cholesterol.

The incidence of hypercholesteremia was 59 per cent in patients over 40 years of age.

Serum cholesterol levels were elevated in 72.5 per cent of patients with arteriosclerosis. Coronary arteriosclerosis showed 69.7 per cent with hypercholesteremia. Approximately the same percentage was established for retinal arteriosclerosis, hypertension and diabetes mellitus.

Although the average serum cholesterol levels of groups treated for from six months to three years by low animal fat diet and desiccated thyroid substance were lower at the end of the period of treatment than at the beginning, the results were not marked or consistent. A low animal fat diet was accompanied by a lowering of serum cholesterol in 55 per cent of individual cases. With the administration of desiccated thyroid substance, and the

combination of low animal fat diet with desiccated thyroid substance, the serum cholesterol level was decreased in approximately 45 per cent of patients in each group.

Reasons for failure to obtain satisfactory evidence of favorable results have been discussed. Further studies are in progress.

BIBLIOGRAPHY

1. Anitschkow, N.: Experimental arteriosclerosis in animals, Chapter X *in:* Cowdry, E. V.: Arteriosclerosis, a survey of the problem, 1933, the Macmillan Company, New York, p. 271.
2. Duff, G. L.: Experimental cholesterol arteriosclerosis and its relationship to human arteriosclerosis, Arch. Path. **20**: 81, 259, 1935.
3. Leary, T.: Atherosclerosis, the important form of arteriosclerosis, a metabolic disease, J. A. M. A. **105**: 475, 1935.
4. Leary, T.: Atherosclerosis. Etiology, Arch. Path. **21**: 459, 1936.
5. Steiner, A., and Kendall, F. E.: Atherosclerosis and arteriosclerosis in dogs following ingestion of cholesterol and thiouracil, Arch. Path. **42**: 433, 1946.
6. Turner, K. B.: Studies on the prevention of cholesterol atherosclerosis in rabbits; effects of whole thyroid and of potassium iodide, J. Exper. Med. **58**: 115, 1933.
7. Turner, K. B., Present, C. H., and Bidwell, E. H.: The role of the thyroid in the regulation of the blood cholesterol of rabbits, J. Exper. Med. **67**: 111, 1938.
8. Fleischmann, W., and Shumacker, H. B., Jr.: The relationship between serum cholesterol and total body cholesterol in experimental hyper- and hypo-thyroidism, Bull. Johns Hopkins Hosp. **71**: 175, 1942.
9. Fleischmann, W., and Fried, I. A.: Studies on the mechanism of the hypercholesterolemia and hypercalcemia induced by estrogens in immature chicks, Endocrinology **36**: 406, 1945.
10. Horlick, L., and Katz, L. N.: The effect of diethylstilbestrol on blood lipids and the development of atherosclerosis in chickens on a normal and low fat diet, J. Lab. and Clin. Med. **33**: 733, 1948.
11. Davis, D., Stern, B., and Lesnick, G.: The lipid and cholesterol content of the blood of patients with angina pectoris and arteriosclerosis, Ann. Int. Med. **11**: 354, 1937.
12. Steiner, A., and Domanski, B.: Serum cholesterol level in coronary arteriosclerosis, Arch. Int. Med. **71**: 397, 1943.
13. Lerman, J., and White, P. D.: Metabolic changes in young people with coronary heart disease, J. Clin. Investigation **25**: 914, 1946.
14. Boas, E. P., Parets, A. D., and Adlersberg, D.: Hereditary disturbance of cholesterol metabolism: a factor in the genesis of atherosclerosis, Am. Heart J. **35**: 611, 1948.
15. Morrison, L. M., Hall, L., and Chaney, A. L.: Cholesterol metabolism; blood serum cholesterol and ester levels in 200 cases of acute coronary thrombosis, Am. J. M. Sc. **216**: 32, 1948.
16. Underdahl, L. O., and Smith, H. L.: Coronary artery disease in women under the age of forty, Proc. Staff Meet., Mayo Clin. **22**: 479, 1947.
17. Turner, K. B., and Steiner, A.: A long term study of the variations of serum cholesterol in man, J. Clin. Investigation **18**: 45, 1939.
18. Page, I. H., Kirk, E., Lewis, W. H., Thompson, W. R., and Van Slyke, D. D.: Plasma lipids of normal men at different ages, J. Biol. Chem. **111**: 613, 1935.
19. Chaplin, G. E.: Serum cholesterol studies in clinical medicine. A thesis. Faculty of Medicine, Queen's University, Kingston, Ont., Can., May, 1946, pp. 29 and 32.
20. Bloch, K., and Rittenberg, D.: On the utilization of acetic acid for cholesterol formation, J. Biol. Chem. **145**: 625, 1942.

21. Katz, L. N., and Dauber, D. V.: The pathogenesis of atherosclerosis, J. Mt. Sinai Hosp. 12: 382, 1945.
22. Gubner, R., and Ungerleider, H. E.: Arteriosclerosis. A statement of the problem, Am. J. Med. **6**: 60, 1949.
23. Steiner, A.: The significance of cholesterol in coronary arteriosclerosis, New York State J. Med. **48**: 1814, 1948.
24. Combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. Cholesterol metabolism and arteriosclerosis, Am. J. Med. **6**: 103, 1949.
25. Anderson, G. E.: Metabolic aspects of vascular degeneration, M. Clin. North America 33: 783 (May) 1949.
26. Leary, T.: Crystalline ester cholesterol and atherosclerosis, Arch. Path. **47**: 1, 1949.
27. Stark, H.: Effect of the rice diet on the serum cholesterol fractions of 154 patients with hypertensive vascular disease, Am. J. Med. **9**: 494, 1950.
28. Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A., and Strisower, B.: Blood lipids and human atherosclerosis, Circulation **2**: 161, 1950.

THE RATIONALE OF GERIATRIC MEDICINE*

By EDWARD J. STIEGLITZ, M.S., M.D., F.A.C.P., *Washington, D. C.*

GERIATRIC medicine, an area of clinical practice, is part of the larger scientific field of gerontology, which is the study of aging. The phenomena and processes of aging affect all things, inanimate as well as living. Geologic structures age, crystals and gels are changed by aging, and cultures and species mature, become senescent and disappear. As biologic aging in an individual begins with conception and terminates only with death, gerontology is properly interested in all phases of life. Growth, development and evolution are just as much associated with the passage of time as atrophy and involution. Both processes continue throughout life. Geriatric medicine, however, is concerned with the clinical problems of later maturity.

Gerontology can be divided logically into three major subdivisions[1]:

(1) *The biology of senescence,* concerned with the mechanisms and processes of aging, focused upon the cell as the unit.

(2) *Geriatric medicine,* dealing with aging men and women, where the individual indivisible, in health and in illness, is the unit with which we deal.

(3) *Sociologic gerontology,* pertaining to the socioeconomic, educational and cultural problems introduced by an aging population.

These three areas are intimately interdependent, pragmatically as well as theoretically. It should be obvious that the more we know about the processes of aging as operative in metabolic, enzymatic and physiologic activities, the more effective the clinical application of geriatric medicine can be. Likewise, the more thoroughly clinical medicine is able to comprehend the changing functional capacities, potentialities and limitations of aging people, the more intelligent sociologic planning can be for the rapidly increasing numbers of the aged among us. And that there is need for intelligence in sociologic planning, no one will deny.

The three perspectives illustrated by this analysis of the immense field of gerontology are equally applicable to any and all problems. In any problem, whether it be war, floods, illness, divorce, marriage, or any other potential catastrophe, we need to apply all three perspectives to obtain comprehensive understanding. First, we need to study the problem with the naked eye; second, we must apply magnification to its component parts and activities; and, last, we must step far enough back that it may be inspected through a reversed telescope, and thus related to its external environment. As medical students, we were all taught that man lives in two environments: the external physical and social world, and the internal milieu of tissue juices, enzymatic activity, anabolism and catabolism. Both environments

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 13, 1951.

are in a constant state of flux and kinetic adjustment. Both are significant to the unitary organism, man.

Translated into other terms, full comprehension of the potentialities of medicine involves three approaches: (1) The indivisible individual, psyche and soma as one, is the unit of study of clinical medicine. (2) Magnification of the component parts, the biochemic reactions, electrical potentials and cellular units which make up the individual, is the concern of the biologic sciences, upon which clinical medicine depends for understanding the entity, man. (3) Man as a member of society, a unit of the external environment, is the concern of social medicine. He is affected by other people, climate, housing, food and threats of disaster, and at the same time his behavior affects his environment.[2]

Geriatric medicine is that area of medical science and practice concerned with the care of the aging and the aged, healthy as well as sick. We are here dealing with *individuals,* not with specific disease entities. These aging and aged individuals are different by reason of their aging, different emotionally and intellectually as well as in their somatic structures and functions. Geriatric medicine is *not* limited to the care of the senile. To so delimit geriatric medicine would be to destroy the major opportunities for accomplishment. It is during early senescence that we may hope to accomplish the most; the truly aged or senile are the terminal consequences of aging. In many respects, the two decades from 40 to 60 are the most critical years. If health be maintained during this phase of later maturity, we may hope for a continuation of health and usefulness.

In order for geriatric medicine fully to develop its potentialities, it must be anticipatory. The potentialities of geriatric medicine are whatever we choose to make them. The obvious limitations to what medical science and practice can do for aging persons must not deter us. We cannot arrest aging without terminating life, for aging is part of living; it is the factor of duration in life. However, the consequences of aging are amenable to retardation and modification. We all know that life expectancy is limited, and that therefore the best clinical results can be but relatively short in duration. But it must not be forgotten that life is multidimensional, that it has depth and breadth as well as mere length. And much can be added to the richness and fullness of life in later years without shortening its duration. There is greater hazard in rusting from disuse than from wearing out from use, as long as we prevent abuse.[3] It is not normal aging which is the urgent challenge, but protracted progressive disablement due to disease. The rising incidence of the chronic disorders typical of later maturity, the so-called degenerative diseases, such as arteriosclerosis, hypertensive disease, diabetes, arthritis, gout, cancer and osteoporosis, is an unfortunate by-product of the dramatic success in prevention and cure of the acute infective disorders of youth. It is by saving the lives of the young that we have advanced longevity from an average expectancy at birth of 47

in 1900 to approximately 68 in 1950. Longevity is here, but not longevity with continued health, vigor and usefulness.

Nowhere is the relativity of health more clearly apparent than in the practice of geriatric medicine. In the fully mature it is quite obvious that there is no sharp line between health and disease. For centuries the physician had been educated and indoctrinated with the concept that his function was to discover, identify and treat *disease*. He was not particularly concerned with the healthy individual. Our code of ethics expected the physician to wait until the patient was sufficiently ill that his awareness of discomfort or functional incompetence drove him to seek medical attention. To build greater health, to prevent illness, to guide individuals in their nutrition and hygiene are attitudes which are now but slowly seeping back into medical philosophy. These were the ideas of the great early Greeks; they disappeared in the era of overwhelming concern with the identification and classification of disease entities and processes. The concepts of anticipatory medicine, of health construction as something more than specific prevention,[4] meet with disheartening inertia on the part of physicians and teachers alike. Only the relatively new fields of pediatric medicine and, more recently, obstetrics, have fully accepted the challenging potentialities of constructive medicine.[5] The indoctrination of many generations of physicians with concern only over disease is not easily corrected. It is harder to unlearn than to learn. As Artemus Ward once said, "Ignorance is not *not* knowing, it is knowing so many things that ain't so."

Health has too long been considered as that state of being existing in the absence of demonstrable disease. Health has quantitative aspects. Perfect, optimal, complete health is an unattainable ideal. Like infinity, it may be approached but never attained. For the sake of clarity in the present discussion, let us define perfect health as that state of being existing when all the functional capacities of the organism are at the maximum which can be expected for the species. In this sense, aging per se, in absence of disease, alters health. For example, at the age at which a "normal" husky lad can run the 100 yard dash most rapidly, his judgment has not yet matured to its maximal capacity. By the time his judgment has developed, his ability to sprint has declined conspicuously. Thus health, in the sense we are employing here, is not only relative but inevitably asymmetric. This is likewise true of age. The asymmetry of aging change is one of the most complex and perplexing aspects of geriatric medicine.

These are some of the things which must be ever in the minds of those dealing with the health of mature persons. We are confronted not with simple single disease entities, but with changing individuals whose functional capacities are asymmetrically developed and variously affected by prior traumata, injuries and experience, and in whom several occult and insidious disease processes are almost inevitably developing concurrently. Here we must discard the notion that our objective is to treat "a disease"; the focus

must be upon *treatment of the person* who may have one or, more probably, more than one disorder. In geriatric medicine it is no longer tenable to treat syphilis or hypertension or diabetes mellitus. We must orient ourselves to the treatment of the syphilitic patient, the hypertensive individual or the diabetic.[6]

Geriatric medicine is not a specialty, in the usually accepted sense of the term. It is my personal hope that it will not become one. It is for this reason that the definitive term is used as an adjective rather than as the noun, geriatrics. Geriatric medicine involves a point of view, or attitude of mind, which takes cognizance of the biologic changes induced by aging. Awareness of the fact that there are changes *alone* is not enough; knowledge of what biochemic, immunologic, nutritional, structural, emotional and intellectual changes occur, and their significance to the biologic economy of the organism, is equally requisite. The diagnostic and therapeutic aspects of geriatric medicine are affected particularly by two groups of factors: (1) the peculiarities characteristic of aging individuals, and (2) the generic characteristics of the disorders most common in later maturity.

To age is to change. Aging and aged persons are not the same individuals they were in their young maturity, just a little older. The changes are insidious, continuous and progressive. The rate of change is greatest in youth and slows with the advancing years. Aging changes are not symmetrical. Pediatrics made its great advance and became a specialized discipline when it was realized that the child is something different from being just "a little man." Though diminutive, the child presents peculiarities of structure, nutrition, physiologic function, immunologic reactions and psychologic attributes which are typical of his phase of development. A similar situation exists in the mature adult, the senescent and the senile. Some may wish it were possible neatly and dogmatically to systematize our knowledge of the changes in relation to age in the later half of life, as Gesell [7] has done with children. However, this is not now possible, and it may never be, for one of the most significant peculiarities of aging is its variability.

With advancing age, increasing divergence between individuals is usual. We are today what we are largely because of the experiences of our yesterdays. The older we become, the more yesterdays have affected us. No two people experience the same infections, nutritional insults, psychic traumata, intoxications, fatigues or mechanical injuries. The inevitable vicissitudes of existence are never identical in content, sequence or severity. The consequences of accumulated injuries, each too minor to be immediately detectable, are inseparable from the similarly variable consequences of aging. Not only do different individuals of the same species vary considerably in their rate of aging, but within the same person aging change is asymmetric. We are not the same biologic age throughout. Certain structures and systems may undergo accelerated aging changes at certain phases of

the life span, whereas the rest of the organism is not so affected. The rapid evolution of the organs of reproduction at puberty and their accelerated involution at the climacteric are illustrative.

As just stated, the consequences of the inevitably accumulated injuries of living and those of aging per se are essentially indistinguishable. Potentially deleterious experiences are unavoidable; to live in a sterile, isolated, ideally protected environment is not living, it is merely existing. It should be emphasized, however, that each potentially injurious or destructive experience, whether somatic or psychic, is likewise potentially beneficial or constructive. For example, fear may be destructive, but at the same time the experience of fear is an absolute requisite to the development of courage. Courage is not absence of fear; this is merely lack of awareness of hazard. Courage cannot be applied without fear. Similarly, in the physical realm, the febrile reaction to typhoid fever vaccination is detrimental to parenchymal tissues, though the benefit of an acquired immunity far outweighs this price.

Diagnosis is greatly complicated by the presence of prior injury and/or impairment. The differentiation of clinical phenomena as being due solely to a recent acute disease, or secondary to preëxisting impairments, often exacerbated by a superimposed acute intoxication, is extremely difficult. This overlapping of several factors likewise affects therapy and prognostication. Exhaustively careful analysis and a high degree of individualization are essential.

The homeostatic mechanisms are altered by aging. The known physiologic constants, such as body temperature, hydration, concentration of glucose, protein and electrolytes in the blood, and the like, all remain the same, irrespective of age (with the single exception of the basal metabolic rate). Normal body temperature is the same at eight days, eight months, eight or 80 years. But the ability to maintain this constancy is less vigorous and less immediate. The hazards of deviation beyond the permissible range of variation are greater. Furthermore, the intensity of symptoms, which are expressions of reaction on the part of host rather than direct manifestations of injury, is greatly reduced, and we must learn to identify and to evaluate minor and very subtle changes. The florid, violent reactions seen in youth are lacking. Geriatric medicine demands the highest type of diagnostic acumen.

Aging affects the response to drugs. There is need for extensive investigation into the pharmacodynamic changes introduced by aging. We know far too little in this area. A reduced tolerance to barbiturates is well recognized. Less generally appreciated are the increasing tolerances to nitrites, alcohol, digitalis preparations and caffeine which often come with aging.

Nutritional requirements change with aging. Some of the changes are known, many merely suspected at present.[8] Fairly clearly defined are the reduced caloric requirements associated with lowering of the metabolic rate,

an increased need for calcium and for protein, and a greatly lessened margin of safety to dehydration. Low-grade deficiencies of vitamins and trace elements, leading to depletion of reserves, are extremely frequent though ill defined. The importance of an optimally high hemoglobin content in the presence of lowered circulatory efficiency cannot be overemphasized.[6]

Psychologic changes introduced by continuing maturation, experience and cerebral circulatory and nutritional impairments are of the greatest significance. In this realm, asymmetry of capacity and functional efficiency can be etiologically responsible for much emotional conflict and stress which may have serious somatic consequences.[9] There is not space here to dwell upon the changes in memory, learning capacity and judgment, and in the exercise of logic, which are part of the normal aging process, but it must be emphasized that not all the changes are necessarily in the direction of decline. Furthermore, there is great individual variation.[6, 10] There are many predictable emotional traumata associated with senescence. To mention but a few, we must include loss of parents, excessive survival of parents, loss of children by maturation, the psychic trauma of mutilating surgery, loss of physical beauty and strength, retirement and the like. Any one of these sources of turmoil is worthy of extended discussion, but time does not permit. It is most important to remember, however, that these are *predictable* traumata which can and should be *anticipated* by the wise clinician so that the damage is kept minimal.

The element of habit is particularly important in geriatric medicine. Habits are created and become fixed by repetition over a period of time. Therefore, with advancing age the rigidity of habit fixation becomes greater. Habits of fluid intake, of work, of eating, sleeping, playing, thinking and dreaming are all important to physical and mental health. Habits may be good, bad or indifferent; the physician must not attempt to alter them abruptly, even if they appear to be undesirable. Abrupt changes are unwise; gradual modification is both safer and more effective. Advice which is ignored is useless. The elderly rightfully feel that if they have survived beyond the usual span, their habits cannot be too detrimental.

The diseases to which geriatric patients are particularly subject differ distinctly from the disorders frequent in youth. Though an older person may acquire any disease, he is typically vulnerable to the so-called degenerative diseases.[11] These include four major groups: circulatory disorders, metabolic disorders, malignant new growths and the arthritides. A much simplified classification shows some of the more pertinent relationships of these disorders:

A. Circulatory disorders
   1. Chronic infective myocardial disease
      (a) Rheumatic
      (b) Luetic

2. Hypertensive arterial disease
3. Arteriosclerosis
   (a) Cerebral: apoplexy
   dementia
   encephalopathy
   (b) Coronary: cardiac disease
   (c) Renal: chronic nephritis
   (d) Pancreatic: diabetes mellitus
   (e) Extremities: gangrene
   Buerger's disease
4. Combination forms

B. Metabolic disorders
1. Diabetes mellitus
2. Anemia
3. Climacteric, female and male
4. Gout

C. Malignant tumors, all forms
D. Arthritides

Of these the first two groups, the circulatory and metabolic disorders are preëminently important. They are so intimately related that attempts to separate the consequences into distinct and isolated disease entities are futile.

The essential differences between the disorders common to youth and those typical of later life are perhaps best contrasted in tabular form:

	Disease in:
Youth	Senescence
Etiology:	Etiology:
Exogenous	Endogenous
Obvious	Occult
Specific (single)	Cumulative
Recent	Distant in time
	Multiple (superimposed)
Onset:	Onset:
Florid	Insidious; asymptomatic
Course:	Course:
Acute	Chronic
Self-limited	Progressive (long disability prior to death)
Immunizing	Not protective (increased vulnerability to other diseases)
Little individual variation	Great individual variation

These contrasting attributes are immensely significant in geriatric medicine. Particularly significant is the fact that the causation of progressive

diseases is largely endogenous and cumulative. These two characteristics make discovery of the etiology very much more difficult than in the obvious infections of youth. It is essential to keep in mind that each individual instance of a given disorder, such as arteriosclerosis, diabetes mellitus or hypertensive arterial disease, results from a series of superimposed factors, and that these factors are rarely identical in any two cases. It would clarify thinking greatly if the singular of the words "etiology" and "cause" were deleted from our vocabularies. Causation is *never* singular. "The cause" of hypertension will never be found. We will never be able to find a single, universal causation responsible for arteriosclerosis.

The overlapping of several superimposed degenerative disorders introduces another significant source of confusion. The physician dealing with a sick child is justified in assuming that the child has only one disease at the moment, and that the patient was essentially well prior to this disorder. He may therefore assume, with a considerable degree of safety, that all the clinical signs and symptoms present are associated with and attributable to this one disease. The physician faced with the problem of diagnosis in senescent individuals, however, must expect the presence of several disorders. Even if the illness is an acute one, he must assume that there probably existed some chronic impairments prior to the onset of the acute disease. Thus he is routinely faced with the problem of deciding which of the physical signs and subjective symptoms are due to the superimposed acute disease and which to preëxisting impairment of health.

The degenerative disorders overlap one another, not only by occurring coincidentally in the same individual, but also in their etiology, pathogenesis and consequences. Such disorders as arteriosclerosis, diabetes mellitus, hypertrophic arthritis, hypertensive disease and the like are too often thought of as precisely demarcated entities. Actually they are not so separable. They present a biologic unity in pathogenesis, in that all of them interfere with the nutrition of parenchymal cells. When we apply nutrition in its broadest sense, and realize that the internal milieu is a nutritional medium, it is not difficult to appreciate that impairments may result from any one or more of these several factors: (1) inadequate nutrition supply (illustrated by dietary deficiencies or anemia); (2) inefficient transport (circulatory impairment); (3) ineffective utilization (such as occurs in diabetes mellitus, hypothyroidism, Addison's disease) and (4) accumulation in the intercellular matrix of detrimental debris (renal decompensation or the edema of cardiac failure).[12]

Conclusion

The essence of the rationale of geriatric medicine can be summarized with a few pertinent dicta:

1. Geriatric medicine, dealing with individuals already past the peak

of maturity, must be concerned with health, both mental and physical, as well as with illness.

2. Health is relative; there is always room for improvement.

3. The aging person changes by reason both of age per se and of the accumulated experiences and injuries inevitable with living; awareness and comprehension of these changing attributes and capacities are essential to the clinician.

4. An attitude of prevention and anticipation is requisite to successful accomplishment; it does not suffice to have hindsight to explain the pathogenesis of disease. Foresight as to what is likely to occur and the recognition of subtle deviations and their potential significance are required for truly good anticipatory or constructive medicine.

5. Geriatric medicine must be concerned with the individual rather than with specific disease entities. Individualization is vitally important.

6. Geriatric medicine does not hope or expect to accomplish miracles. Not infrequently the maintenance of a status quo in health for an individual with progressive illness is a major therapeutic accomplishment. We fight delaying actions. We must expect to lose every patient ultimately. Nevertheless, the field is full of challenge and reward. The gratitude of the elderly for the fact that someone is sufficiently interested to listen patiently and is anxious to assist is pathetic. Here we deal with subtle insidious changes, demanding the highest diagnostic acumen for their detection, identification and evaluation, and the greatest therapeutic skill individually applied. Geriatric medicine is no area for those who are intellectually lazy.

BIBLIOGRAPHY

1. Stieglitz, E. J.: The orientation of geriatrics, Geriatrics **4**: 127, 1949.
2. Galdston, I. (Editor): Social medicine: its derivations and objectives, 1949, Commonwealth Fund, New York.
3. Stieglitz, E. J.: The second forty years, 1946, Lippincott, Philadelphia.
4. Stieglitz, E. J.: A future for preventive medicine, 1945, Commonwealth Fund, New York.
5. Stieglitz, E. J.: Pertinent problems of geriatric medicine, Ann. Int. Med. **18**: 89, 1943.
6. Stieglitz, E. J. (Editor): Geriatric medicine: the care of the aging and the aged, Ed. 2, 1949, W. B. Saunders Company, Philadelphia.
7. Gesell, A., and Ilg, F. L.: The child from five to ten, 1946, Harper and Brothers, New York.
8. Stieglitz, E. J.: Nutrition problems of geriatric medicine, J. A. M. A. **142**: 1070, 1950.
9. Stieglitz, E. J.: Factors contributing to mental disease in the aged, J. Gerontol. **2**: 280, 1947.
10. Kaplan, O. (Editor): Mental disorders in later life, 1945, Stanford University Press, Stanford, California.
11. Stieglitz, E. J.: Medicine in an aging population, M. Clin. North America **33**: 295 (March) 1949.
12. Stieglitz, E. J.: Difficulties in the clinical recognition of degenerative diseases, Biological Symposia XI, Aging and degenerative diseases, Edited by R. Moore, 1945, Jacques Cattell Press, Lancaster.

THERAPY OF TRAUMATIC SHOCK*

By BENJAMIN BURBANK, M.D., F.A.C.P., *Brooklyn, New York*

DIAGNOSIS

THE experiences of the past war have shown how very difficult it is to define by exact criteria just what constitutes the condition of shock. The end stage, in which the patient has no perceptible blood pressure or pulse, is pale with a gray cyanosis and cold with clammy perspiration, represents a medical defeat in diagnosis. Attempts to delineate a definite blood pressure level, such as 70 mm. Hg, have serious drawbacks because the end stage as described above may take place within a matter of minutes after such a reading. The same objections hold true for determining the tendency of the patient's blood pressure either to rise or fall. Following the work of Blalock,[1] Moon,[2] and others, the hematocrit was used as the most delicate guide of impending shock. If accepted too rigidly, this also is disappointing. The author found that, when 500 determinations of the hematocrit were made in a series of seriously wounded patients, shock was immediately impending or present when the hematocrit was in the low anemic, normal or high concentrated levels. In the shock of trauma, hemodilution and hemoconcentration are complicated by the added factors of serocavitary contamination, cold, exposure, pain and exhaustion, all of them possible individual etiologic factors for the production of the shock syndrome. Instead of attempting to define this syndrome, the patients should be classified as seriously wounded. This group either presents overt evidence of shock or, from the nature of their wounds, they are considered to be in a state of impending shock. It might even be wise to regard these individuals as cases of "compensated shock," in whom decompensation may occur at any moment. The ones most apt to fall into this group are those with penetrating wounds of the abdomen, chest or skull, or involvement of a major blood vessel, or major fractures of the long bones. Because shock intervenes so rapidly and frequently in such individuals, any delay in therapy is dangerous to life or limb. The problems presented by these severely injured patients include the resuscitation from existing shock, an effort at possible stabilization, and the preparation necessary to enable them to withstand the further trauma of the necessary operative procedures.

TRIAGE

Abdominal injuries always deserve the highest priority, since they are all cases of potential peritonitis. When the peritoneum is soiled, it is

* Received for publication February 7, 1951.
From the Department of Medicine, State University Medical Center at New York, College of Medicine, and the Long Island College Hospital, Brooklyn, New York.

believed that a period of six hours represents the maximal time before irreparable damage occurs. Whether this latent interval can be prolonged by the use of antibiotic agents effective against the coliform organisms is highly doubtful. It does not seem likely that the degree of soiling encountered in these cases can respond to anything short of adequate surgery. Since a good part of the golden six hours will be used in transporting the patient to the hospital, very little time remains for the necessary resuscitative measures. Having been brought out of shock these cases must be operated on immediately. In instances in which operation had to be delayed because of inadequate facilities, such patients sank into a second period of shock for which all measures were unsuccessful. The operating schedule must be so planned that tables are available for these cases at all times.

Deserving an equal priority with the abdominal cases are those injuries in which active bleeding is a major factor or in which there has been a major vascular injury. The impairment of circulation to a wound which is already contaminated means that gas gangrene or other grave infection is an ever present danger. On the other hand, injuries to the thoracic cage will rarely constitute a surgical emergency problem. The shock in these cases is due to a seriously disturbed cardiorespiratory function.[3, 4] Infection does not pose any immediate, serious threat to survival. Hemorrhage sufficient to induce shock occurs in less than 1 per cent of the cases with chest injuries who survive to reach the First Aid Station.

In general, it may also be said that intracranial injuries do not deserve an urgent surgical priority. In most instances there is an external wound, so that cases with increased intracranial pressure are rare. Here, too, the prevention of infection does not depend on a very stringent time schedule.

With the use of widespread and adequate splinting of major skeletal injuries "where they lie," the percentage of such patients in shock is relatively small. When serious hemorrhage ensues, this usually can be easily controlled with a tourniquet and does not require immediate operative intervention.

Therapy

The measures designed to resuscitate these gravely wounded patients are those known to neutralize the various factors which have been shown to induce shock. In general, the important factors are an altered circulatory volume, a disturbed cardiorespiratory mechanism, dehydration, infection, pain and exposure.

Infection

To combat infection, antibiotics should be started early and vigorously. Where a large volume of patients is expected, it is wise to utilize the services of an antibiotic team whose function it is to inject each patient at regular intervals. In the past war, penicillin was given in 25,000 unit doses every

three hours day and night. Every patient received this routinely unless he was tagged as not requiring such therapy. In the interests of economy of personnel, it may be just as efficacious to use procaine penicillin, giving a dosage of 300,000 units every 12 hours. In view of the excellent reports that have appeared concerning the value of the other antibiotics in controlling infections due to the coliform and gram-negative organisms, it seems quite certain that streptomycin, aureomycin and chloromycetin will also play valuable rôles. The work of Jawetz,[5] however, suggests that the latter two may have antagonistic results when combined with penicillin. It would seem that the wisest course would be to initiate a program of penicillin combined with streptomycin, and that the other antibiotics be held in reserve for use in specific instances.

Exposure

Exposure was a major factor for the infantry living under miserable conditions over a prolonged period. It does not seem likely that it will be important in civilian injuries. For all major injuries reaching the hospital, the standard procedure is to cut away all garments and then gently and swiftly place the patient between warm blankets on a clean litter. The foot of the litter should be elevated eight to 12 inches. This procedure is considered so important that it is the first step in the resuscitative program.

Pain

Irrespective of the validity of the neurogenic theory of shock, there is no doubt that pain is a real factor in inducing and perpetuating the syndrome. The marked reduction in mortality following early and adequate splinting in fractures of the femur illustrates this vividly. There is no doubt that seriously wounded patients, facing a painful and arduous evacuation, require adequate sedation. Morphine answers this need best of all, because of both its efficiency and ease of administration. Yet it has given rise to a high incidence of serious complications, as pointed out by Beecher.[6] Casualties with major injuries are all too frequently in such a degree of shock that the impaired peripheral circulation fails to absorb the drug from its subcutaneous or intramuscular site. Since the pain persists because of failure of absorption, repeated doses are given. With adequate resuscitation complete absorption occurs, and then all too frequently the signs of overmorphinization appear and increase the difficulties of both preoperative and postoperative management of the patient. In such instances, and perhaps even as a routine measure, it is better to give smaller doses of morphine intravenously. Experience has shown that doses of one-eighth and one-quarter grain of morphine, given intravenously, are by far the most efficient method of administration. The maximal effect is quickly obtained, and so dosage can be more adequately gauged. Some of these patients will have

been overdosed with morphine during their transportation to the hospital. Following successful resuscitative measures, the signs of morphine intoxication may rapidly appear. The best treatment in such instances is the use of coramine, given intravenously in a dosage of 5 to 10 c.c. The results are dramatic.

Fluid Replacement Therapy

The major portion of the resuscitative scheme, however, is concerned with proper replacement of fluid. This introduces the problems of the type of fluid to be used, the quantities to be given, the maximal effects to be expected, the period of time in which such improvement can be expected, and the dangers associated with this type of therapy. The problem is particularly acute in patients with serious abdominal injuries, because two opposing factors play a part in establishing the patient's clinical status. On the one hand, a serious loss of blood usually occurs and tends to produce hemorrhagic shock; whereas, peritoneal contamination tends to produce hemoconcentration. Both factors must be adequately treated to obtain the best results. In the early days of the war, when whole blood was not freely available and large volumes of plasma were used, many patients could be brought out of shock temporarily but were unable to withstand the subsequent operative procedure and died of hemorrhagic shock. Even concentrated serum albumin was very disappointing in this respect. With the use of whole blood, dramatic improvement resulted.

In patients with serious abdominal injuries there is always a substantial amount of blood lost. In many cases this is external, and no adequate evaluation can be made. When intraabdominal bleeding occurs one can gain a rough idea of the amount of blood lost. Unfortunately, this cannot be used as a index by the shock teams, since even this is an unknown quantity in the preoperative phase. Routine determinations of blood pressure have not been of much help. Half of the patients had blood pressure in the normal range, while in the other half the blood pressure was usually unobtainable. In the first group, when operative intervention was undertaken without preliminary resuscitative measures, shock invariably ensued during the procedure. Later in the series, hematocrit readings were routinely obtained in an effort to secure a more precise evaluation of the patient's condition. About half of the patients with abdominal injuries had hematocrit readings which ranged from 35 to 50 per cent. This would appear to be a range in which operative intervention could be undertaken safely. Again all too frequently disaster resulted. In many of these patients, in spite of their having hematocrits in the range of 40, operation disclosed intraperitoneal collections of bloody fluid ranging from 1,500 to 4,000 c.c. In those cases widespread peritoneal contamination was also present. It would thus appear that massive contamination tends toward hemoconcentration, which may obscure the results which uncomplicated hemorrhage is expected to

produce. Table 1 tabulates the clinical status of 10 patients with abdominal wounds admitted to a field hospital and illustrates the varying initial pictures they present.

This does not mean that serial clinical evaluation, blood pressure and hematocrit readings are not of the utmost importance in the program of precise resuscitation of the patients with serious abdominal wounds. It was found routinely that attempts at major abdominal surgery in individuals with a preoperative hematocrit of less than 35 were always associated with serious operative shock. On the other hand, it was also found that, when the large amounts of whole blood given during the preoperative and operative management of the patient resulted in hematocrits of 45 and above, such patients were apt to have a stormy postoperative course. A high incidence of peripheral collapse and anuria developed. Where serial hematocrits could be obtained, they were of great value in determining the necessary volume of fluid to be administered in hemorrhagic shock. Thus, if a patient was admitted with a hematocrit of 20, and 1,500 c.c. of blood caused an increase to a level of less than 35 but there was progressive increase of the hematocrit, it was considered wise to give more blood before submitting the patient for operation. For example, a patient was seen two hours following a penetrating wound of the abdomen. Blood pressure and pulse

TABLE I

Admission Status of Patients with Major Abdominal Wounds

Name	Preoperative								Injury
	Time of Injury	Previous Plasma	Exam. Time	B.P.	Pulse	Hb.	Hematocrit	Plasma Protein	All cases were acutely ill.
1. H. O.	1900	0	2130	112/70	80	14.9	44	7.2	Retroperitoneal hematoma.
2. C. A.	1100	0	1405	120/80	100	15.5	45	6.8	Two perforations of cecum.
3. L. C.	1600	0	1845	124/100	120	17.2	51	7.4	Laceration of liver and gallbladder. Laceration of small and large intestines. Extensive peritoneal contamination.
4. D. H. D.	?	1,250	1500	130/80	110	14.6	43	6.2	Extensive wounds of splenic colon. Evisceration.
5. W. N.	?	250	1015	140/100	96	16.8	50	7.2	Small and large intestine wounds. Abdominal wounds.
6. D. A. E.	?	0	1830	0/0	0	14.4	42	6.5	Evisceration of small and large bowel. Minimal wounds of large bowel.
7. A. A. L.	?	750	1820	100/60	140	10.5	36	6.2	Wounds of large bowel with massive peritoneal contamination.
8. D. G.	1600	0	1730	70/30	Thready	11.8	34	5.1	1,500 c.c. blood in peritoneal cavity.
9. R. J. R.	?	250	2100	0/0	0	11.8	35	7.2	Massive hemoperitoneum. Liver wound.
10. N. J. V.	?	1,000 blood 750	2130	50/40	128	11	33	7.9	Liver wound.

were unobtainable. Admission hematocrit was 22. Within the next hour he was given 1,500 c.c. of blood by pumping it in. The blood pressure rose to 130/80. Hematocrit at this time was only 28. Over the next hour a further 1,500 c.c. of blood were given. The blood pressure remained stable and the hematocrit rose to 37. At operation, 4,000 c.c. of bloody fluid were found in the peritoneal cavity, and there were extensive wounds of the spleen and a laceration of the colon. The patient withstood the operative procedure well and made an uneventful recovery.

In contradistinction to this is the patient who receives apparently adequate amounts of fluid and still fails to respond to the resuscitative program. An example of this is a case admitted with a perforating wound in the left upper quadrant of the abdomen and a penetrating wound at the apex of the left chest, with accompanying compound fractures of the left clavicle and first rib. On admission, the blood pressure was 40/20 and the pulse imperceptible. In the next three hours he was given 3,500 c.c. of whole blood. The pulse was then recorded at 170 per minute, and the blood pressure at 70/40. A hematocrit taken at this time was 21, and the hemoglobin was 7.5 gm. Operation revealed active hemorrhage from a laceration of the intrathoracic portion of the subclavian artery and vein.

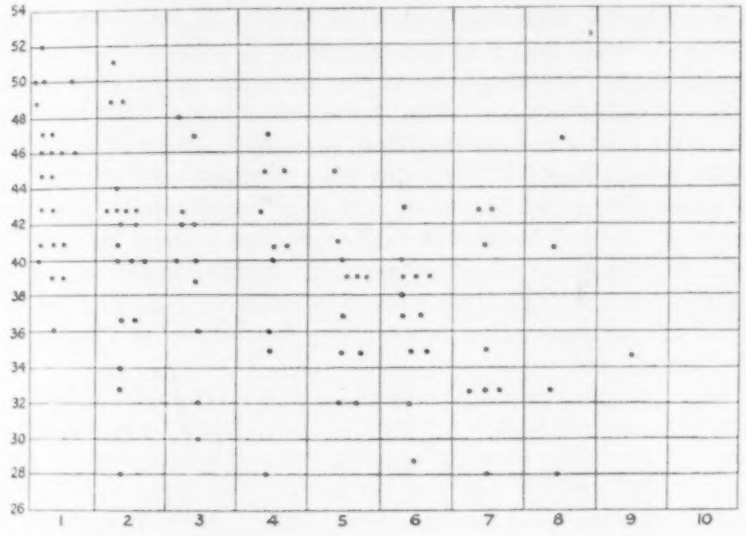
With experience, it was felt that the pendulum had perhaps swung too far in favor of whole blood and that there was still a definite and valuable place for the use of plasma. This was borne out by the observation that, in patients who succumbed, serial hematocrits revealed a progressive increase, though this increase did not necessarily rise above the normal range for an uninjured individual. Furthermore, most patients improved somewhere between the fourth and sixth day postoperatively, and it was noted that this improvement occurred concomitantly with a drop in the patient's hematocrit. This is illustrated in table 2.

Thus, toward the end of the war, larger amounts of plasma were used preoperatively and during the operation, and particularly in the postoperative phase. The value of plasma is dramatically illustrated in the following case.[7] L. T. received a high explosive fragment wound of the right side of the abdomen at 4:30. Seven hours later he received 250 c.c. of plasma. Nine hours after the injury he was admitted to the hospital. At this time his blood pressure was 120/80 and his pulse 82 per minute, but he was acutely ill. Five hundred cubic centimeters of whole blood were given and he was admitted for operation three hours later. The pulse at this time was 190 per minute and the blood pressure 120/80. In the next 15 minutes, 500 c.c. of plasma and 500 c.c. of blood were given and the pulse dropped to 140 per minute. During the next hour, while under operation, he received an additional 1,000 c.c. of plasma and 500 c.c. of blood. At this time the blood pressure was 100/70 and the pulse 120 per minute. Operation had revealed extensive damage to the right colon, with widespread peritoneal soiling. A red blood cell count at this stage was 6,500,000.

The operation lasted another hour, during which an additional 1,000 c.c. of plasma were given. At the conclusion, the pulse was 120 per minute, the blood pressure 110/70 and the red cell count 4,500,000. Fifteen minutes after the patient returned to the ward, the blood pressure suddenly dropped to 40/0 and no pulse could be obtained. The red cell count at this point had increased to 7,500,000. Immediately, 1,250 c.c. of plasma were pumped into the veins (in about 30 minutes). At this point the red blood cell count dropped to 4,500,000 and the blood pressure rose to 170, with a good strong pulse. Plasma was continued as a constant intravenous drip (50 drops per minute) until 10,000 c.c. were given. Eight hours

TABLE II

Postoperative Serial Hematocrits in a Group of Patients with Abdominal Injuries Revealing Tendency to Hemodilution in the Fourth and Fifth Days Postoperative When a Concomitant Clinical Improvement Occurred



postoperatively the patient was in good condition, with a stable blood pressure and a good pulse. Repeated blood counts revealed 4,500,000 red blood cells. On the second day postoperatively the patient developed some ascites, which gradually subsided. On the fifth day postoperatively he developed small bilateral effusions. Thoracentesis yielded 300 c.c. from the left side and 100 c.c. from the right side. On the ninth day his condition was so good and stable that he was evacuated to the rear without any difficulty.

Unfortunately, it was impossible to obtain hematocrits in this case, but from the value of the red blood cell counts and the extensive soiling of the peritoneum it seems reasonable to assume that real hemoconcentration existed. In this instance, plasma was forced far more than whole blood,

and in the postoperative period it was used exclusively. From experiences with similar cases it was felt that undoubtedly it was responsible for the successful outcome in this case. In another case, in which similar amounts of plasma were used, ascites and pleural effusion also occurred and these may have been due to transudation of the plasma from the unstable capillary bed. They are, however, complications which can be managed.

As a result of such experience, it seems certain that cases with major wounds of the abdomen would yield definite evidence of anemia when first seen. If the hematocrit is in the normal or slightly subnormal range, hemoconcentration should be suspected. Such patients should have vigorous preoperative treatment regardless of their blood pressure and their apparently good clinical condition. It would also seem that, while they do require some whole blood to replace that lost externally, the main replacement therapy should consist of plasma.

One of the big problems of resuscitation is the decision as to when the patient is ready for operation and, even more important, when the preoperative observation indicates that operation is imperative if the patient is to survive at all. Keeping in mind that six hours is said to be the golden period for operation in cases with abdominal wounds, we found that the indications were a return of the blood pressure, pulse and hematocrit to reasonably normal levels. When this was obtained early, it was also felt that the patients benefited by a short period of "stabilization," during which the reasonably normal blood and cardiac dynamics could repair to better advantage the ravages of tissue anoxia. If the time lag between wounding and operation was too great, no attempt was made to stabilize the patient. Since there are no comparable controls, this consideration of stabilization is a purely theoretic point.

When a patient failed to manifest a proper clinical response to the resuscitative measures within a period of three hours, it was decided that there was either active bleeding or such gross contamination of the peritoneal cavity that surgical intervention was the only hope of correcting the process. Such cases were then given the highest priority for operation, in spite of their poor condition.

What, then, constitutes the ideal resuscitative management of abdominal wounds? Every effort should be made to restore the blood pressure and pulse to approximately normal levels. The blood should be studied on admission and the proper regime for replacement of fluid started. If the clinical picture, blood pressure and pulse are normal but the blood picture is not, the proper corrective measures must be instituted before submitting the patient to operation. Another determination of the blood count should be made within two to three hours. If there is no improvement, operation is indicated immediately. If the trend is in the proper direction and the six hour period has not elapsed, it might be wise to give the patient a small period of stabilization. Just what constitutes a safe blood reading is un-

known. It would seem that when anemia is found initially, the use of enough whole blood to raise the hematocrit to 35 or above is sufficient to permit the patient to withstand a major surgical procedure. When the initial hematocrit is in the relatively normal range, there is usually a concomitant normal blood pressure; yet this group frequently gives great difficulty during the operative and postoperative stages. Thus, more plasma should be given along with whole blood preoperatively, in an endeavor to arrest or reverse the tendency to hemoconcentration.

In general, patients with abdominal injuries required about 1,500 c.c. of whole blood and 1,000 c.c. of plasma during the preoperative stage and similar amounts during the operative stage. Routine postoperative orders consisted of the daily administration of 500 c.c. of plasma, 1,000 c.c. of 5 per cent glucose and saline, and 1,000 c.c. of 10 per cent glucose in distilled water.

Dehydration and disturbed balance of the electrolytes did not seem to be a problem in the preoperative and operative scheme. Since no adequate clinical studies were made, it may be that we are overlooking factors of great importance which could further improve the results. Certainly the maintenance of hydration and nutrition in the postoperative management of abdominal wounds is of the greatest importance, since all this must be controlled by the parenteral route. The problem did not seem to be any different from that encountered in the routine postoperative management in civilian practice.

Skeletal Injuries

Fluid replacement therapy rarely offered a serious problem in the treatment of patients with major fractures. When hematocrit determinations were made on such a group of patients, it was immediately apparent that major blood loss was the outstanding phenomenon. These patients as a rule came in with marked pallor or with unobtainable blood pressure and pulse. In every instance, the use of whole blood very quickly restored them to normal physiologic levels. In reviewing this group of patients it was found that they required an average of 1,500 c.c. of whole blood preoperatively and about 1,000 c.c. of whole blood during the operative stage. Although plasma was used, it averaged about 500 c.c. during both the preoperative and operative stages.

Thoracic Injuries

In stark contradistinction, cases with thoracic injuries offer a very serious difficulty in selecting the proper therapy for replacement of fluid. Here, the essential cause of shock is an altered cardiopulmonary function, which imposes a serious burden on the pulmonary circulation. The administration of fluids parenterally may easily result in a fatal outcome. Fortunately, hemorrhage is practically never severe enough to produce hemorrhagic shock. In a series of 1,000 major thoracic wounds, only two in-

stances were encountered in which active bleeding played any rôle. When the hilar blood vessels are torn, patients die before any aid can reach them. This is probably also true when the subclavian or internal mammary vessels are torn. Persistent bleeding from lacerations of the intercostal vessels does not occur. In the patients who underwent operation there were innumerable instances of laceration of the intercostal vessels, but these were always retracted and did not present any active bleeding. Table 3 summarizes the status of 10 unselected patients with major thoracic wounds. It illustrates that hypotension and serious loss of blood were rarely encountered in these cases.

TABLE III

Admission Status of Patients with Major Thoracic Injuries

Name	Preoperative								Injury
	Time of Injury	Previous Plasma	Exam. Time	B.P.	Pulse	Hb.	Hematocrit	Plasma Protein	All cases were acutely ill and had at least one sucking wound of chest.
1. H. P.	2115	0	2215	110/70	88	14	41.5	5.8	Perforating wound of chest.
2. J. W. E.	0930	250	1230	110/80	96	9.5	28	5.8	Penetrating wound of chest.
3. J. L. B.	?	250	1730	80/40	?	10	29	6.2	Perforating wound of chest.
4. C. W. D.	0900	1,000	1400	130/80	110	9.5	28	7.5	Perforating wound of chest.
5. R. E. B.	?	500	1735	70/50	?	11	33	6.5	Perforating wound of chest. Transverse myelitis D7.
6. T. A. Y.	1445	750	1700	100/50	144	13.2	39	6.5	Penetrating wound of chest.
7. J. K.	1500	0	2015	102/70	120	12.2	36	7.2	Penetrating wound of chest.
8. C. E. F.	1070	250	1600	110/70	120	13	39	6.8	Mediastinal emphysema. Perforating wounds of both chests.
9. J. P. H.	0730	0	1030	130/80	96	15	44	6.8	Perforating wound of chest.
10. A. C. A.	0500	0	1045	140/70	132	16	47	7.5	Perforating wound of chest.

Because of the excellent blood supply of the thoracic wall, early infection does not occur, and there is no stimulus for hemoconcentration. Liberal amounts of plasma can serve no useful purpose. The prime emergency, then, is to restore a normal cardiorespiratory function without adding to the hazards by unnecessary therapy with fluids.

It is felt that the following probably represents the modus operandi of shock in thoracic injuries. Whether the initial insult is due to blast, contusion, penetration or perforation, vagal impulses are set up which produce bronchorrhea and bronchospasm. Thus, when patients are seen early they present a picture of dyspnea and cyanosis associated with coarse, dry and moist bronchial râles. In some instances they appear to be having an attack of bronchial asthma. This sequence of events produces anoxia in the distal alveoli. The response to anoxia is increased transudation of serum across the alveolar capillary membrane. At this stage, cyanosis and dyspnea are increased and the patient has a persistent, moist but ineffectual cough. Even

when he raises sputum the wet cough persists. Anoxia is further increased by the pain of the injury, which splints the thoracic wall and restricts the respiratory movements. In addition, there is frequently an accompanying pneumothorax or hemothorax which further depresses the vital capacity by mechanical compression of the lung. In many cases of low chest wounds, a further complication is the presence of a vastly distended stomach. Because of anoxia, these patients are extremely apprehensive and restless.

Unnecessary movements add another burden to the already distressed circulation. Unfortunately, this restlessness is so serious that there is a great temptation to quiet the patient by the liberal administration of narcotics. This can only lead to further serious complications. The narcotics depress the respiratory center and seriously impair the cough reflex. Yet these patients have wet lungs which can only be drained by means of effective coughing. In many instances, in an effort to alleviate pain and splint the accompanying fractured ribs, tight strapping is used. This practice should be condemned completely. It is unphysiologic in that it impedes respiration. In addition, it is rarely effective. Indeed, in some instances relief was obtained by removing the tight strapping. Pain is best relieved by either intercostal or paravertebral sympathetic block with novocaine.[8] This simple procedure forms one of the major mainstays in treating serious thoracic injuries. It alleviates pain more effectively than morphine or strapping. Thus respiratory movements become more efficient. Usually, with the relief of pain, the patient can even be encouraged to cough in such a manner that he can expectorate his secretions effectively. Nerve block has one other very important consideration: by interrupting the pain impulses, it probably neutralizes the noxious stimuli which produce the vagal overactivity. This would seem to be borne out by the fact that, in many patients, the use of simple nerve block interrupted the whole vicious cycle of the wet lung and restored patients to a normal physiologic status in a very short period of time.

Of equal importance with nerve block is the prompt and vigorous administration of oxygen. In dealing with very large numbers of casualties it is quite obvious that the oxygen tent is not feasible. The use of a mask is also not successful, because of inadequate facilities for proper application of the mask and because many patients with marked apprehension will not cooperate. The ordinary nasal airways are very inefficient. A No. 12 or No. 14 nasal catheter, with a few additional perforations, inserted well into the oropharynx is the most efficient and the simplest means for giving oxygen therapy.

In many patients, in spite of adequate nerve block and oxygen therapy, the wet lung will persist. This is most apt to occur when patients are treated late, and it is usually due to the fact that they are too exhausted to clear their secretions properly from the respiratory passages. In such instances, these secretions may be aspirated by the insertion of the tracheal

catheter, first in the trachea and then in both major bronchi.[9] This is a simple therapy which does not require any cumbersome equipment or unusual technical skill. It has proved to be truly life-saving in a high percentage of cases. At times, however, even this will not be sufficient adequately to clear the tracheobronchial tree. In such instances, bronchoscopy must be used. These patients are often desperately ill and indeed appear to be moribund, so that one frequently has the impression that they will not be able to withstand the further strain of bronchoscopy. It should be stressed, however, that the more desperate the situation, the greater the necessity for such drastic measures.

The third step in the resuscitative scheme for thoracic shock is the removal of all abnormal mechanical pressure. In the presence of a "silent lung," thoracentesis should be done immediately and the collection of air or blood aspirated vigorously. In many standard texts, it is still stated that this is a dangerous procedure, in that the pneumothorax and hemothorax act as a tamponade and prevent further bleeding. Experience has shown that this concept is fallacious. Early and vigorous aspiration of the pleural cavity restores the function of the lung, diminishes the incidence of empyema and does not add to the hazard of recurrent bleeding. In this respect, in low thoracic wounds, if a distended stomach is found, a Levine tube should be inserted and the stomach decompressed.

The following case is a good example of the success that may be obtained when such a plan of management is followed. The subject was wounded by a high explosive fragment, sustaining a penetrating wound of the right chest on June 28, 1944, at 6:00 p.m. Fifteen minutes later, at the Battalion Aid Station, sulfanilamide powder was dusted into the wound and he was given six tablets of sulfadiazine and 0.5 gr. of morphine sulfate. At the collecting company, a diagnosis of sucking wound was made and an occlusive dressing applied. He was then given 250 c.c. of plasma and 150 c.c. of blood. Four hours after injury, he was given another 0.25 gr. of morphine sulfate. Within 15 minutes he was comatose, and a bloody froth was exuding from the nostrils. Orthopnea and cyanosis were marked and the respirations, which were 20 per minute, were sucking and irregular and audible moist râles were present. No blood pressure or pulse could be obtained. A tracheal catheter was inserted immediately and a large amount of the frothy sputum was aspirated, with marked improvement. However, the pulmonary edema kept recurring, so that the tracheal catheter was left in site and aspirations were performed every half-hour. In the intervals between aspirations, oxygen was delivered via the catheter. Four hours later, the blood pressure was 90/50 and the pulse 104. A thoracentesis of the right chest yielded 150 c.c. of bloody fluid and an intercostal nerve block was performed. The patient was now markedly improved. However, two hours later the blood pressure began to fall and the respirations slowed, so that within one hour the blood pressure was 70/50, the respira-

tions decreased to eight per minute and coma supervened. Six centimeters of coramine were given intravenously to counteract the effects of the morphine and there was dramatic improvement. One-half hour later the patient was actually restless, the moist râles were entirely gone from the lungs, and the tracheal catheter was removed. Two hours later, the blood pressure was 114/70 and the pulse 100. These resuscitative measures took nine hours, and the patient was then removed over 30 miles of rough road to the nearest evacuation hospital. He withstood the trip quite well.

How long should this scheme of management be followed? There is no urgency in operating on thoracic injuries for the following reasons:

(1) The lung is bruised and contused and is incapable of normal inflation and deflation. If early thoracotomy is performed, the lung cannot expand to occupy the entire pleural cavity. Thus a dead space is left, which forms an excellent nidus for the production of an empyema. In addition, oozing from the contused surface continues for many hours or days even after operation is performed. The addition of blood to the dead space furnishes an excellent medium for the propagation of bacteria. Thus early thoracotomy increases the incidence of empyema.

(2) The chest wall itself is highly resistant to infection, so that debridement may be delayed for many hours or, if necessary, even for a few days.

(3) The lung has enormous capabilities for self-healing. Thus early resection of the injured pulmonary tissues is contraindicated.

(4) Active hemorrhage is a very rare occurrence.

(5) Retained foreign bodies do not produce suppuration or bleeding in the early stages. It is better to wait until the lung has regained its normal motility before removing these. Thus it was routine for thoracotomies to be performed about two weeks after injury in order to remove retained foreign bodies.

In view of these facts, the resuscitative measures should be continued until the patient is restored to a normal cardiopulmonary status. In actual practice this usually took from eight to 24 hours, although in one instance it required five days. During this period fluids were limited to a total of about 1,500 c.c., consisting of about 1,000 c.c. of plasma and 500 c.c. of blood. Subsequent to this, the patient is finally transferred for operation.

Blast

It has been reported that the Hiroshima and Nagasaki bombings produced a large incidence of blast injuries. However, very few details as to the accuracy of this diagnosis have been presented. During the blitz of London similar reports appeared. The British War Office undertook extensive investigations into this subject. They found that the vast majority of so-called blast injuries were incorrectly diagnosed.[10] A true blast injury is characterized by shock with severe pulmonary changes, in the

absence of any external evidence of injury. In a high percentage of such cases there will be concomitant abdominal pain and rigidity, and ruptured ear drums. In actual experience, the British found that most of the patients were injured by secondary missiles, such as masonry, wood, glass, etc., or by being hurled with great force against a hard surface. The clinical features in such cases would be similar to those described with battlefield wounds.

The physiologic disturbances and pathologic lesions in cases of true blast injuries in both experimental animals and human subjects have been reported in great detail by the British investigators.[11] The most typical injury is hemorrhage in the lung, which varies from small scattered hemorrhagic spots to hemorrhagic consolidation of an entire lobe or lung. An accompanying hemothorax or pneumothorax may be present. Histologically, there is rupture of the alveolar walls with hemorrhages from torn alveolar capillaries. The alveoli and smallest bronchioles are filled with blood, and these may coalesce and fill the larger bronchi, leading to consolidation or atelectasis of an entire lobe. Hemorrhagic lesions are also present in the abdomen. These are specially evident in the large intestines and muscles of the abdominal walls, and only rarely involve the liver or spleen. The clinical features consist of shock, dyspnea, cyanosis, thoracic and abdominal pain, cough and expectoration. Following initial survival, these symptoms persist for about 10 days. The gravest complication is the development of a superimposed pneumonia. In some cases, abdominal pain and rigidity are the predominating features. It is generally believed that this pain is referred from the thorax. Laparotomy should never be performed in blast injury unless there is positive proof of intraabdominal trauma, such as laceration of the liver or spleen. This should consist of signs of severe hemorrhagic shock which do not respond to treatment with large volumes of whole blood. The pulmonary picture closely resembles that previously described as wet lung. The British concluded that oxygen and rest are essential. Venesection was frequently life-saving. The addition of intravenous fluids should be avoided, as it so frequently leads to severe pulmonary edema. General anesthesia and operation should be postponed as long as possible. From this description it seems highly likely that blast lung is another variation of the traumatic wet lung seen so frequently in military casualties. It follows, then, that similar therapy should be recommended for the treatment of these blast injuries.

Summary

1. The nature of the wound, rather than the immediate clinical status, should determine whether a patient requires treatment for shock.

2. Abdominal injuries, active hemorrhage and wounds with impaired circulation always deserve the highest surgical priority.

3. Replacement of fluid is the major therapeutic problem in patients with serious wounds.

4. Serious blood loss usually occurs with abdominal injuries but, because of concomitant peritoneal contamination, the clinical picture may be confusing. Both whole blood and plasma must be given liberally to restore these patients and to enable them to withstand operation.

5. When cases with abdominal wounds fail to respond to adequate replacement of fluid within a period of three hours, either persistent hemorrhage or massive peritoneal contamination is present. Even in the face of the direst clinical picture, surgical intervention offers the only hope for possible survival.

6. Thoracic injuries are best treated by a program of: (a) Local nerve block, to control pain and encourage coughing. Morphine and tight strapping should be avoided. (b) Oxygen therapy, which should be started as soon as possible and maintained until a normal cardiorespiratory status is established. (c) Maintenance of an open tracheobronchial tree. If an effective cough reflex cannot be obtained, aspiration with a tracheal catheter is urgently indicated. In severe cases, bronchoscopy may be life-saving. (d) Intravenous fluids, which should be administered with great caution. The overburdened circulation may fail completely with additional loads. (e) Immediate correction of abnormal intra-pleural pressures, by the vigorous aspiration of abnormal collections of air and fluid in the pleural or gastric cavities. (f) Postponement of operation and anesthesia as long as possible.

BIBLIOGRAPHY

1. Blalock, A.: Principles of surgical care; shock and other problems, 1940, C. V. Mosby Co., St. Louis.
2. Moon, V. H.: Shock and related capillary phenomena, 1938, Oxford University Press, New York.
3. Burford, T. H., and Burbank, B.: Traumatic wet lung, J. Thoracic Surg. **14**: 6 (Dec.) 1945.
4. Brewer, L. A., Burbank, B., Samson, P. C., and Schiff, C. A.: The wet lung in war casualties, Ann. Surg. **123**: 343 (March), 1946.
5. Jawetz, E., and Speck, R. S.: Joint action of penicillin and chloramphenicol on an experimental streptococcic infection of mice, Proc. Soc. Exper. Biol. and Med. **74**: 93–96, 1950.
6. Beecher, H. K.: Morphine poisoning in battle casualties, Medical Bulletin, NATOUSA **1**: 22 (Feb.) 1944.
7. Dry, J.: Personal communication.
8. Fitzpatrick, L. J., Adams, A. J., and Burbank, B.: Nerve block in the treatment of thoracic injuries, Medical Bulletin, NATOUSA **2**: 51–53 (Sept.) 1944.
9. Samson, P. C., Brewer, L. A., and Burbank, B.: Tracheobronchial catheter aspiration, Bull. U. S. Army M. Dept. **5**: 227 (Feb.) 1946.
10. Hadfield, G. et al.: Differential diagnosis of lung injuries, Lancet **2**: 197–199 (Aug. 16) 1941.
11. Zuckerman, S., and others: Discussion on problems of blast injuries, Proc. Roy. Soc. Med. **34**: 171–192 (Jan. 6) 1941.

MYOCARDIAL INFARCTION IN A RURAL HOSPITAL *

By Francis F. Harrison, M.D., F.A.C.P., *Cooperstown, New York*

Since the introduction of anticoagulant drugs in the therapy of myocardial infarction there has been a continued effort to assess their value accurately. The study having the widest scope is that sponsored by the American Heart Association.[1] In this large series much effort was expended toward trying to achieve adequate controls. Even so, possible sources of error have since been pointed out by Doscher and Poindexter.[2] This and other papers have served to clarify the question as to what factors are important in determining the mortality rate in myocardial infarction.

For some years we have been interested in myocardial infarction as seen in the Bassett Hospital, an institution serving a highly rural community. It has seemed that there were certain differences between our experience and that of urban hospitals. The initial observations offered in 1938 on a very small group of cases [3a] made only two points: first, that, as contrasted with an urban series, infarction occurred a decade later, and second that the disparity in the incidence in men and women was much smaller in the rural series.

The age incidence is of great importance as a factor in mortality, and it is thought in this case to be dependent upon the extraordinary age distribution in the area served by this hospital. In Otsego County in 1930 the proportion of persons over 60 years of age had reached a figure which the Division of Vital Statistics of the New York State Department of Health had estimated the State would reach in 1965. It was thus shown by De Porte [3b] that Otsego County had already reached and probably passed the level at which the State as a whole, in its process of aging, would reach a generation later.

The present series comprises 236 cases seen between 1932 and 1950. In determining inclusion in the group, the verdict of the pathologist was of course accepted. Without this confirmation it was insisted that there be unequivocal evidence in either the clinical picture or the electrocardiogram, with the other being compatible. No cases were included in which more than 21 days had elapsed between the apparent date of infarction and hospital admission. Table 1 shows the gross mortality and average age incidence. The date groupings are arbitrary, being dependent on the first study made in 1938 and on the date when anticoagulants were first used. They serve a purpose, however, in that they suggest a mortality trend independent of age incidence. A gradual decline in mortality is followed

* Received for publication December 6, 1950.
From the Medical Service of the Mary Imogene Bassett Hospital.

by a sharp drop coincident with the use of anticoagulant drugs. Since 1948, all patients have been treated with anticoagulants as soon as the diagnosis of myocardial infarction seemed reasonably well established. All treated cases were included, even if they died within an hour or two after the institution of anticoagulant therapy. Six cases seen since 1948, in which the diagnosis was not made until autopsy, did not seem to belong in either the treated or untreated group. In order to compensate for the error thus introduced, the 14 similar cases from the untreated group were also put in the same separate category. These 20 cases were for the most part elderly individuals in whom the terminal event was masked by other serious disease, or instances in which the patient died before adequate examination could be carried out.

In the majority of cases both heparin and Dicumarol were used. A prothrombin determination was done at the time this therapy was instituted. Heparin was given deep subcutaneously in 50 mg. doses, the time interval

TABLE I

Myocardial Infarction, Mary Imogene Bassett Hospital

		Cases	Av. Age	Deaths	%
Untreated Group	1932–1938	30	62	21	70
	1938–1946	78	62	37	47
	1946–1948	35	64	15	43
	Total	143	63	73	51
Anticoagulant Group	1946–1950	73	59	13	18
Undiagnosed Group	1932–1950	20	68	20	100
	Total	236	62	106	45

between injections being regulated by determinations of the venous clotting time. Heparin was discontinued as soon as the prothrombin levels were within therapeutic range. Prothrombin determinations were done daily, and an effort was made to keep the prothrombin concentration around 30 per cent of normal. Undiluted plasma was used for prothrombin determination, and the results were reported both in seconds and as the index compared to a control. The results checked closely as long as the same control was used, but a variation of as much as three or four seconds occasionally was encountered when it became necessary to use a new control. In a few cases, hemorrhagic manifestations were encountered, most often hematuria. They were readily controlled by the injection of 70 mg. of synthetic vitamin K. At no time was it necessary to abandon anticoagulant therapy altogether because of hemorrhagic manifestations, but in several instances it seemed wiser to finish the course of therapy with the prothrombin level higher than the optimal one. Dicumarol was continued until the patient's discharge from the hospital, usually five to six weeks after admission. The first case of myocardial infarction to be treated at this hospital

with anticoagulants received heparin by continuous intravenous drip for nine days after two severe embolic episodes. This patient recovered and has been at almost full activity for the last four years.

The distribution of our cases by age and sex is graphically shown in figure 1. The ratio of males to females is 1.9 to 1, as contrasted with 3.7 to 1 in the 1917 cases collected from the literature by Doscher and Poindexter.[2] A series having a sex ratio more nearly comparable to ours is that of Billings et al.[4] in which the males predominate as 2.7 is to 1. Their figures are evidently derived from a mixture of urban and rural cases, the exact composition not being stated. The only explanation for the variation in sex ratio which seems at all tenable is that our unusual distribution is dependent upon the older age of the group. As is shown and is well known, the peak incidence occurs at an older age in women than in men. Possibly any group of infarctions in older people would have a more equal distribution

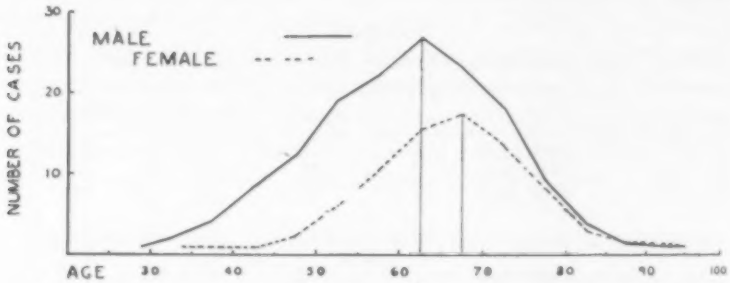


FIG. 1. Age and sex incidence of 236 cases of myocardial infarction.

between men and women. The figure also shows that the peak incidence occurs a decade late, as compared to the data of Doscher and Poindexter.[2]

We have been particularly interested in the high mortality in our control series. Similar figures are reported by Billings et al.,[4] who quote an immediate mortality of 54 per cent among patients living in rural areas, as compared to 35 per cent among patients living in cities, and 58 per cent in farmers, as compared to 30 per cent among professional men and tradesmen. The authors explain these differences by the fact that the percentage of the urban group brought to the hospital within 24 hours after the onset of the attack was twice that of the rural patients. Thinking that this factor might have some bearing on our changing mortality, we have in table 2 contrasted the data from the earliest group of cases with the most recent ones, those treated with anticoagulants. It is evident from these figures that patients with myocardial infarction are now reaching the hospital earlier than they were 12 to 18 years ago. From the same records it was also possible to make a rough estimate that the diagnosis was suspected before admission in 48 per cent of the early group and in 72 per cent of the anticoagulant group.

It seems probable that the training of the referring doctors is of importance in determining how early in the disease the patient reaches the hospital. In the early years of this series, the majority of the rural practitioners belonged to an older generation not well indoctrinated in the clinical picture of myocardial infarction. They have subsequently been largely replaced by a younger group, better schooled in this diagnosis.

Another factor believed to contribute to our high mortality is the rugged independence of many of our patients, a trait which occasionally works out to their disadvantage. The following case is an example in point.

Case Report

A 60 year old farmer walked into the author's office with the classic story and appearance of acute myocardial infarction, confirmed by electrocardiogram. No amount of persuasion could induce him to stay in the hospital, and four days later he was up milking. At this time a pericardial friction rub was heard. Eventually he spent several weeks in bed. Seven months later he was seen at home with a second infarction, complicated by ventricular tachycardia, and he then consented to come to the hospital. The author got stuck in a snowdrift in front of the house and to his horror discovered the patient helping to push him out. The patient died six hours later. Autopsy showed extensive myocardial infarction, with a large mural thrombus filling an aneurysmal dilatation of the anterior wall of the left ventricle.

Table II

Time After Onset of Admission to Hospital

	1932–1938	Anticoagulant Group
First 24 hours	48%	69%
Second 24 hours	14%	21%
Later	38%	10%

It seems safe to assume that this type of treatment did not improve the patient's chances of recovery. Less dramatic examples are not rare in our files and are presumed to contribute to the high mortality. They seem to be getting less common in recent years, although we have no actual figures to support this impression.

No attempt has been made to break the series down into first and later infarctions. This was because the series seemed too small and also because such figures have been proved to be most inaccurate. It is highly probable that in many instances unrecognized previous infarction had occurred.

The contrast in mortality between the group treated with anticoagulants and the untreated group is very striking, but misleading. It is obvious that the untreated group is not a satisfactory control series. For example, the average age is four years younger in the treated group. Also, it already has been shown that patients with myocardial infarction in the last two years are being referred to the hospital sooner after onset, and it is believed that their treatment before admission is more adequate. In recent years the referring doctor has usually given the diagnosis on the telephone and discussed the optimal time for transportation. This is very different from

the practice of delivering, often without warning, an undiagnosed, moribund patient.

Another reason for regarding the untreated group as an inadequate control series is the fact that the use of multiple precordial leads and unipolar limb leads has considerably increased our assurance in diagnosis. As a matter of fact, the marked reduction in mortality corresponds about as well in point of time to this development as it does to the use of anticoagulants. A review of the electrocardiograms in the 73 treated cases reveals 10 instances in which the diagnosis could not have been made with assurance from the standard limb leads. Using the same criteria, there were six instances in the original 32 cases in which myocardial infarction was proved at autopsy and yet the electrocardiograms were not diagnostic with the leads used at that time. Whether or not one has much faith in the present therapeutic measures, there would seem to be a definite advantage in establishing an early diagnosis. As early as 1932, Coombs [5] noted that the prognosis was improving coincident with increasing accuracy in early diagnosis. Considering all the factors discussed, it seems relatively certain that the mortality rate in myocardial infarction would have declined to a certain extent in the past two years even without the use of anticoagulants.

TABLE III

Thromboembolic Complications
Percentage

	No.	Extension	Embolism	V. Thrombosis
Untreated Group, 1932–1950	163	7.4	19.0	4.3
Anticoagulant Group, 1946–1950	73	1.8	8.2	0

On the other hand, analysis of the incidence of thromboembolic complications as given in table 3 indicates a significant reduction. The change may be somewhat greater than this table indicates because the index of suspicion has certainly been increased since the introduction of anticoagulant therapy, and presumably the clinical diagnosis is less often missed. The reduction in thromboembolic complications can certainly be credited to anticoagulants. How much more is open to question.

SUMMARY

1. A series is presented of 236 cases of myocardial infarction observed in a rural hospital over an 18 year period.

2. The series showed a high age incidence and a relatively large proportion of women.

3. The immediate mortality rate was originally high, dropped slowly over a period of years, then fell rapidly coincident with the use of anticoagulant drugs.

4. Evidence is advanced to indicate that the rapid lowering of mortality was in part due to factors other than the use of anticoagulants.

5. There was a significant reduction in thromboembolic manifestations coincident with the use of anticoagulant drugs.

BIBLIOGRAPHY

1. Wright, I. S. et al.: Report of the Committee for the Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis with Myocardial Infarction, Am. Heart J. **36**: 801, 1948.
2. Doscher, N., and Poindexter, C. A.: Myocardial infarction without anticoagulant therapy, Am. J. Med. **8**: 623, 1950.
3. Rural Medicine, Proceedings of the Conference held at Cooperstown, New York, October 7 and 8, 1938. (a) Heart Disease in a Rural Community. (b) Demography of Otsego County.
4. Billings, F. T. et al.: Prognosis of acute myocardial infarction, Am. J. Med. **7**: 356, 1949.
5. Coombs, C. F.: Prognosis in coronary thrombosis, Bristol Med.-Chir. J. **49**: 277, 1932.

PAIN IN ACUTE AND CHRONIC DISEASES OF THE LIVER*

By Howard P. Lewis, M.D., F.A.C.P., *Portland, Oregon*

The symptoms and signs of liver disease have suffered from underemphasis in recent years as sharper focus has been brought to bear on the greatly expanded knowledge of the physiology and laboratory methods of study of this organ. Nevertheless, careful analysis of the history and physical findings still remains essential for the early recognition of liver disease and its complications, and for the evaluation of many facets of its progress. In this respect, liver pain is highly important. It is interesting to note how often scant attention is paid to the liver as a source of abdominal pain. Actually, no differential analysis of pain in the abdomen, particularly in its upper half, is complete without careful consideration of the liver as its source. The fact that hepatic pain is often not characteristic or different from pain due to many other causes does not invalidate the innumerable instances in which it is sufficiently clearcut to be very important in diagnosis.

Pain arising from the extrahepatic biliary system has been studied extensively. Its causes, variations and radiation are well defined. The causes of liver pain, and therefore many of its distinguishing characteristics, are poorly understood and subject to dispute. Much of this difficulty stems from our incomplete knowledge of the nerve supply of the organ. Some clarification of this has been made in recent years, and for this reason it is advisable to review our present understanding of the subject.

Innervation of the Liver (figure 1)

Many inaccuracies in older studies of the innervation of the liver have been corrected by more recent investigations with improved technics.[2, 4, 5, 6] Nerves supplying the liver and bile ducts are grouped into an anterior and posterior hepatic plexus. The anterior plexus lies in close association with the hepatic artery, the posterior at the posterior aspect of the portal vein. The anterior plexus is the smaller and is composed of sympathetic postganglionic fibers whose preganglionic counterparts arise from T 7–10. The former begin in the left celiac ganglion and are joined by preganglionic fibers from the right abdominal branch of the left vagus. Parasympathetic branches from this plexus are distributed to the cystic duct and gall bladder, and some contribute to the *Nervus pancreaticocholedochus*. Other branches join with the posterior plexus, enter the hepatic portal and ramify in the liver in connection with the hepatic artery and the bile ducts. The posterior

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 11, 1951.

From the Department of Medicine, University of Oregon Medical School, Portland, Oregon.

plexus includes a group of postganglionic sympathetic fibers from the right celiac ganglion. These also have their preganglionic origin in T 7–10. A branch from the right vagus traverses the right celiac ganglion and gives preganglionic fibers to the plexus. Parasympathetic and sympathetic branches from this plexus extend to the gall bladder and common bile duct. The remaining fibers are distributed within the liver in a way similar to the branches of the anterior plexus. Vagus fibers to the gall bladder and bile

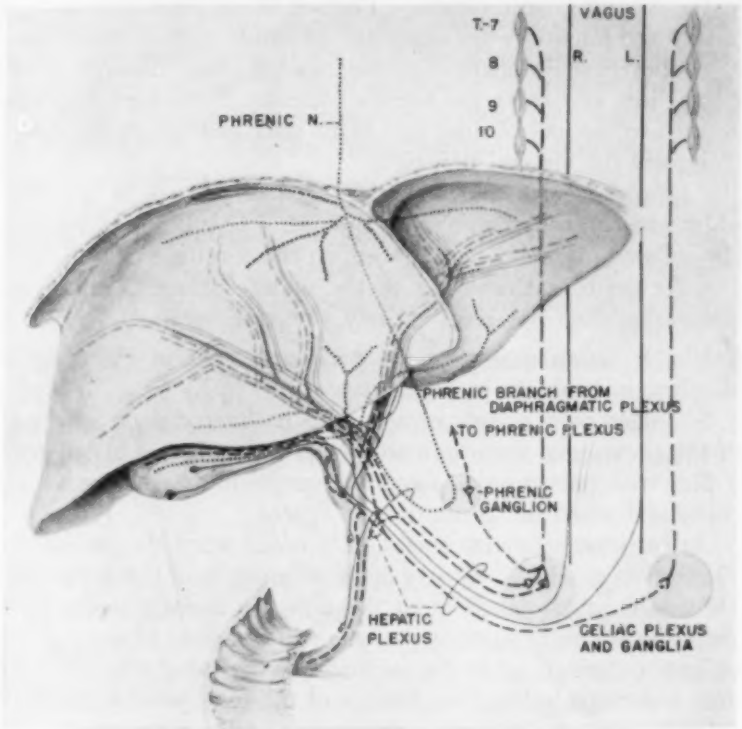


FIG. 1. Diagram of innervation of liver (after Alexander, Kuntz, Raigorodsky and others). Sympathetic afferents follow pathways of pre- and postganglionic sympathetic efferents. Distribution of phrenic afferents to liver capsule suggested by some reported observations, but not proved by histological study.

ducts for the most part synapse with ganglion cells in the walls of these structures or in the nearby tissues.

Vagus and sympathetic fibers accompany the arteries and bile ducts throughout the liver. Innervation of the arteries is exclusively by the sympathetics. The bile ducts are innervated as far peripherally as smooth muscle extends, apparently by both the parasympathetic and the sympathetic. Sympathetic afferent fibers seem to exist, but there is no evidence of the presence of parasympathetic afferents. Nerve fibers within the hepatic

lobules or nerve endings around the hepatic cells have not been demonstrated with certainty.

Data obtained by degeneration experiments, anatomic dissections and peritoneoscopy indicate that afferent fibers of the right phrenic nerve are, in some individuals, distributed to the coronary and falciform ligaments, to some parts of the capsule of the liver at least, the gall bladder and within the liver itself.[4, 6, 7] When this is true, branches of the right phrenic nerve, after giving off fibers to the under surface of the diaphragm, mingle with fibers of the diaphragmatic plexus. Phrenic fibers from this plexus supply the coronary and falciform ligaments and probably part of the adjacent liver capsule. Other phrenic fibers continue onward, pass through or near the phrenic ganglion, and enter the hepatic plexus. From here they appear to be distributed to the gall bladder and cystic duct and within the liver, where they accompany the visceral nerves.

Right supraclavicular and shoulder tip pain occurs in some cases of gall bladder and parenchymatous liver disease. This has been assumed to be caused by inflammation of or traction upon the coronary and falciform ligaments, or the peritoneal covering of the under surface of the diaphragm. This explanation does not seem entirely adequate because:

(1) Visible inflammation of the peritoneal coat of the under surface of the diaphragm is absent in hepatitis.

(2) Shoulder pain occurs occasionally in liver disease in the absence of much enlargement of the organ and when the patient is at bed-rest.

(3) Referred pain to the shoulder has been noted in some cases of biliary colic and when the cystic duct is ligated.[8]

(4) At peritoneoscopy no sensation is noted when the peritoneal covering of the liver is touched. Biopsy from the margin of the liver causes little pain. If the biopsy is taken from the anterior surface of the right lobe, 2 to 4 cm. from the margin, many patients will complain of sharp diffuse pain over the liver anteriorly or in the midback on the same side, when the nose of the biopsy forceps indents the surface of the liver prior to perforating it. Perforation sometimes produces even sharper pain for an instant. Electrocoagulation of the biopsy area may cause pain that is persistent for several hours. In addition to the pain described, nearly 20 per cent of patients complain of pain in the right shoulder area at the same time. These manipulations are not believed to have caused traction on the hepatic ligaments sufficient to cause pain.[7] In spite of incomplete anatomic data, the evidence cited above suggests that painful sensations from the capsule, gall bladder and cystic duct arise, in some people, from phrenic nerve endings existent there.

Observation that cutting, burning or pinching the liver substance does not cause pain in the conscious patient has led to the belief that the hepatic parenchyma is insensitive to pain, and that therefore hepatic pain must be due to acute stretching of the capsule or traction on the hepatic ligaments.

While this undoubtedly is often true, as a sole mechanism for hepatic pain it seems improbable for the following reasons:

(1) Wolff and Wolf state that such a sweeping conclusion is not warranted by the evidence and that the matter of pain threshold might be important. In their work on visceral pain,[1, 2] they found that the normal mucosa of the stomach, bowel and bladder was insensitive to selected stimuli. When the mucosa of these structures was congested or inflamed, the original stimuli then caused pain, sometimes of considerable intensity. This indicated that the threshold for visceral pain could be lowered by inflammation or congestion, as in the case of the pain threshold of the skin. While no information concerning the effect of hepatic inflammation or engorgement on the threshold of possible pain receptors in the liver parenchyma is available, the possibility is great that a similar mechanism operates in this organ. Since there is evidence of the presence of phrenic afferents within the liver, it is possible that shoulder pain, under favorable circumstances, could be due to parenchymal changes alone. Clinical observation tends to confirm this.

(2) Liver pain occurs in diseases such as acute hepatic necrosis, when the liver is actually smaller than usual and capsular tension therefore diminished.

(3) Liver pain is present in atrophic cirrhosis wherein capsular stretching, if present, would be local and slow in onset.

(4) Pain is felt in some cases of central hepatoma or abscess before there is significant local stretching of the capsule or noticeable enlargement of the organ.

Liver Pain

Is pain a symptom of any importance in the diagnosis of liver disease? Is it of value in following the progress of established liver disease? These questions can best be answered by an analysis of the symptom as it is actually encountered in some of the more important parenchymal diseases of the organ. The terms "abdominal distress" and "abdominal discomfort" often appear in the literature of liver disorders. These rather meaningless statements do emphasize that such sensations as fullness, tightness, feelings of weight, distention or mild aching pain in the abdomen are exceedingly common with liver disease. Liver disease can also cause severe pain which may, in turn, be accompanied by abdominal rigidity and tenderness to a degree that suggests extrahepatic inflammation or even perforation of a viscus. Proof for this is furnished by surgical operations not rarely undertaken under such circumstances.

The following descriptions of liver pain will serve to emphasize specifically the preceding general discussion. These are based upon personal observation both in and out of Military Service, the records of the University Hospitals and Clinics, and information gleaned from representative sampling of the vast literature.

Hepatitis

Abdominal pain is one of the important symptoms of hepatitis. It occurs more frequently in infectious than in serum hepatitis.[9] Pain is common in the pre-icteric stage [9, 10, 11, 12, 13] in the form of a dull ache or a painful, dragging sensation in the epigastrium or upper right abdomen. The pain may be constant or intermittent, and exercise, jolting, jarring, bending forward, heavy meals or breathing often intensify it. In some instances of acute onset, the pain may be so severe or unusually located as to suggest acute appendicitis, cholecystitis, perforated viscus or, when intermittent and colicky, gall-stone colic. Failure or inability to recognize the cause in these instances has led many times to undesirable surgical intervention.[9, 10, 12-17, 24] When the liver is not enlarged or tender at this stage the problem of diagnosis is sometimes insoluble. Bilirubinuria, frequently present in hepatitis before clinical icterus, is a helpful clue, as are the systemic manifestations. Fist percussion over the organ will often cause pain, which typically appears after a latent period of several seconds and gradually increases in severity for three to five seconds. The ache may persist for some time afterward.[13, 22] This is a helpful sign.

Pain sometimes is first apparent with the onset of icterus or, if present before, becomes so intense as to suggest bile duct obstruction. Light colored stools at the onset may be further confusing. Upper abdominal rigidity is sometimes marked. At this stage, generalized, steady or colicky abdominal pain may appear. The cause of this kind of pain is not certain. Some observers [10] feel it is the result of a sudden rise in intraportal pressure secondary to liver swelling and endophlebitis of the portal radicles in the liver. Simple reflex intestinal cramping or edema of the mesentery and bowel wall might account for some of this distress.

Pain in the right shoulder, apparently from reference via the phrenic nerve, is seen occasionally. This is known to occur in the absence of significant enlargement of the liver or evidence of perihepatitis. It may be that this is the result of the parenchymatous inflammation; when present, it adds a note of confusion to the clinical picture because of its known association with inflammatory processes under the diaphragm.

A malignant form of hepatitis has been described [16, 17] which is characterized by a protracted, severe course, frequency in women and high mortality. Pain was present in about half the cases and was predominantly felt in the right hypochondrium. A number of the more severe cases, especially the fatal ones, had extremely severe pain under the right costal margin that was often intermittent and colicky. Laparotomies were performed on five of these patients because the pain was thought to be due to gall-stones. No stones were found.[16]

All who have had experience with the delayed recovery of hepatitis, or the symptoms of chronic hepatitis, recognize the importance of pain as a gauge of recovery, relapse or chronicity. Numerous writers have referred

to this.[9, 10, 12, 13, 18, 19, 20, 21, 22, 24] Aching, sharp epigastric or right upper abdominal pain, appearing in the erect position or with exercise during the convalescent phase of acute hepatitis, usually indicates incomplete recovery and the need for further bed-rest. This reaction may occur for a long time after apparent clinical recovery. The other symptoms commonly seen—lassitude, fatigability and poor appetite—often lead, in the absence of definite confirmatory signs of organic disease, to a diagnosis of psychoneurosis. Such a conclusion is frequently justified, but very often this complaint is due to continuance of the liver injury. The incidence of relapse is so frequent in patients with this syndrome that a functional label should be applied with great caution. The mechanism of this particular complaint is not well understood. Its rapid onset and the frequent coincident enlargement and tenderness of the liver suggest acute congestion as the cause. However, studies in normal man show a considerable fall in estimated hepatic blood flow in the upright position and after exercise,[23] apparently due to splanchnic and hepatic vasoconstriction. This argues against congestion as the cause, as does the occasional persistence of pain after several days of bed-rest. Further studies are necessary to clarify this point.

Increased pain over the liver or in the epigastrium appearing in the course of an otherwise uncomplicated hepatitis may mark the onset of acute hepatic necrosis or an exacerbation of the disease. In the early stages of acute hepatic necrosis, as in acute yellow atrophy from other causes, the pain may be of great severity and followed within hours by nervous system symptoms which so frequently usher in coma. Such a change in symptoms is frequently misinterpreted because, at the time, the patient's condition may not clearly suggest the rapid deterioration that will follow.

The factors contributing to pain in hepatitis are seen to be not well defined. Undoubtedly distention of the capsule causes some. However, this seems inadequate as an explanation in cases that do not have significant liver swelling or tenderness. This precept also falls short in hepatic necrosis, because rapid shrinkage of the liver occurs at a time when pain may be marked. Reflex intestinal disturbances, mesenteric and intestinal edema undoubtedly contribute, but there remains the excellent probability that some and perhaps much of the pain is due to inflammation of the hepatic parenchyma.

Cirrhosis of the Liver

Very few cases of portal cirrhosis are totally without complaints before the appearance of jaundice or ascites. Careful probing will usually bring out symptoms of the disease that may antedate these complications by many years.[10, 25, 26, 27] Pain is a frequent early symptom.

Pain accompanies portal cirrhosis in nearly half the cases. In two-thirds of these it is located in the epigastrium, over the liver or in the right hypo-

chondrium.[10, 28, 29, 30] Radiation of pain to the shoulder has also been observed, but less frequently than in hepatitis.[10, 25] The pain complained of is usually a dull ache, frequently difficult for the patient to describe and localize well. It is often intermittent and may be aggravated by exercise or food. If jaundice appears, it is often heralded by an increase in pain or the appearance of pain for the first time.

Severe pain may occur with cirrhosis, of a degree to suggest a surgical emergency for which operations have been done. Colicky pain is not uncommon and, in view of the known tendency of cirrhotics to develop gallstones, presents a difficult problem in diagnosis.[10, 28, 31] This colicky pain has been thought to be due to transient edema or hyperemia of the liver.[10] All grades of pain may occur, with or without accompanying enlargement or tenderness of the organ, although in cases complaining of severe pain the liver is often tender.

The pain described above is alone not diagnostic of the disease. Enlargement of the spleen and other familiar associated symptoms, as weakness, weight loss and fatigability, help classify the pain and help in the recognition of many cases of cirrhosis in the pre-ascitic stage.

Generalized abdominal pain, seen often in cirrhosis, presents another problem. As causes, increase in intraportal pressure, occlusion of mesenteric veins, displacement of other organs or intestinal dysfunction secondary to stasis in the portal circulation have been suggested.[10, 29] The fact that pain is a prominent complaint in some patients during the onset of ascites suggests that portal system changes are important factors.

It is difficult to see how, in a disease accompanied by scarring and deformity of the liver, capsular tension due to liver swelling could regularly account for pain. It seems likely that tissue and circulatory changes within the organ must have an important part in the pain mechanism.

Nonobstructive biliary or cholangiolitic cirrhosis, in some cases thought to be of viral origin,[32] is characterized by longstanding regurgitation jaundice, recurrent attacks of fever and upper abdominal pain. The hepatosplenomegaly and frequent occurrence of clubbed fingers help distinguish this type.

Primary Carcinoma of the Liver

Pain is an outstanding symptom of primary carcinoma of the liver, whether it be hepatoma or cholangioma.[10, 33, 34, 35, 36, 37, 38] Except in the young, these tumors occur in association with cirrhosis of the liver in a high percentage of cases. For this reason the symptoms of cirrhosis frequently precede those of the tumor, and the latter's manifestations may appear to be only complications of the cirrhosis. Pain is very often the initial symptom of the tumor and may be noticed before its other signs (tumor, enlarged liver, rapidly accumulating ascites, jaundice) appear.

Dull pain in the hepatic area or epigastrium is usual, but extremely severe pain may occur. The author has personal knowledge of one case in which the pain and tenderness over a rapidly enlarging hepatoma was so severe that the tumor was needled in the belief that it was an abscess. Radiation of pain to the back is not rare, and referred pain to the shoulders has been observed. Pain in the points of radiation may precede abdominal pain and can, in these circumstances, present a very confusing picture.[33, 34, 39] One case observed had sudden, severe, shifting pain in the back of such intensity that dissecting aortic aneurysm was suspected for several days.

Pain in some cases is due in part to distention of the liver capsule.[33] Some observers believe perihepatitis[10] is principally responsible. Neither idea is tenable in all circumstances, because pain may be present with tumor in a cirrhotic liver that is not enlarged and does not show perihepatitis. Pain on breathing may be experienced if perihepatitis is present. The marked spread of some of these tumors through the liver with resulting damage to the parenchyma, blood vessels and bile ducts may have an important rôle in the production of pain. Hemorrhage into the tumor, which is common, sometimes with rupture into the peritoneal cavity, probably accounts for some of the sudden, acute exacerbations of pain that are encountered.

Secondary metastatic carcinoma, because of its usually well localized, slow growing and fairly circumscribed tumors, is not often a cause of significant hepatic pain. More symptoms ordinarily arise from the primary site of the carcinoma than from the liver.

Abscess of the Liver

Indefinite systemic symptoms, including chills and fever, usually precede pain in single or multiple pyogenic liver abscesses, sometimes for several months.[43] Eventually, about 90 per cent of pyogenic abscesses are accompanied by pain, which is therefore one of their outstanding symptoms.[10, 40, 41, 42, 43, 44] In the earlier stages the pain is usually dull, constant and felt over the liver, especially anteriorly or in the axillary line, or in the epigastrium. Sharp, severe pain, many times aggravated by breathing, is common in the later stages, and is probably in part due to perihepatitis. Abdominal rigidity may be marked in the more severe cases. A striking feature of this condition, which is important, is the low incidence of nausea, vomiting or other reflex disturbances ordinarily seen with other inflammatory diseases in the upper abdomen.

Since the vast majority of pyogenic abscesses are located in the right lobe of the liver, especially in its anterior or superior aspect, most pain is felt here. Points of radiation include the midback, right loin and the right shoulder area. Shoulder pain often appears to be due to direct inflammatory involvement of the inferior surface of the diaphragm, as is indicated by the occurrence of secondary pleural effusions.

Localized intercostal pain, frequently accompanied by spot tenderness, is common if the abscess lies close to the surface. This complaint and finding, when present together, are highly significant. Liver enlargement is frequent, as is tenderness.

Steady pain over the liver area, local tenderness, chills, fever and mild gastrointestinal symptoms characterize a solitary abscess. Multiple abscesses and pylephlebitis tend to have milder and less well localized pain and tenderness, and a higher and more septic type of fever with multiple severe chills and sweats.

Pain is the most common and one of the earliest local evidences of amebic abscess or hepatitis.[10, 46] Pain is present in more than 75 per cent of the cases.[46] In contrast to pyogenic abscess, pain in amebic abscess has a slower onset and is often less intense. The pain is usually dull and aching, but can be severe. Localization of the pain follows the same general rules as pyogenic abscess. Abscess in the left lobe may cause left upper abdominal and shoulder pain and is more frequently accompanied by gastric disturbances.

Shoulder pain in this condition is most often due to diaphragmatic irritation by an abscess in the dome of the liver. This complaint is very common and occasionally is the most prominent one. As in pyogenic abscess, perihepatitis may cause symptoms. Spot tenderness to finger pressure will often localize the area.

Sudden thrust of the finger on the liver, quick compression of the thoracic cage or a sharp, mild blow over the liver may cause, as in hepatitis and pyogenic abscess, a deep seated, aching pain that persists for a short time. This finding is of considerable diagnostic importance.

The symptoms and laboratory evidence of *Endamoeba histolytica* infestation are, when present, obviously exceedingly important in distinguishing between pyogenic and amebic abscess.

Summary

Pain is a useful and important symptom of hepatic disease. As a symptom it is helpful not only in early recognition of the condition but also in evaluation of its progress and complications.

Studies of innervation of the liver indicate that it is supplied by sympathetic fibers arising from T 7–10 bilaterally, the right and left vagus and, in some instances, by branches of the right phrenic nerve. Evidence for the presence of intrahepatic phrenic afferents is presented and their rôle in pain production is discussed.

Characteristics of pain as encountered in hepatitis, cirrhosis and carcinoma of the liver and liver abscess are presented. Study of the pain pattern in these conditions indicates it is frequently clear enough to be of assistance in diagnosis and prognosis. The probable point of origin of pain in these diseases is discussed and the significance of shoulder pain in liver disease is commented upon.

BIBLIOGRAPHY

1. Wolff, H. G., and Wolf, S.: Pain, American Lecture Series, 1948, Charles C. Thomas, Publisher, Springfield, Illinois.
2. Wolf, S., and Wolff, H. G: Human gastric function. An experimental study of a man and his stomach, 2 Ed., 1947, Oxford University Press, New York.
3. Kuntz, A.: The autonomic nervous system, 1945, Lea & Febiger, Philadelphia.
4. Alexander, W. F.: The innervation of the biliary system, J. Comp. Neurol. **72**: 357, 1940.
5. Gray, H., and Goss, C. M. (Ed.): Anatomy of the human body, 1948, Lea & Febiger, Philadelphia.
6. Raigorodsky, J. L.: Die Nerven der Leberpforte des Menschen, Ztschr. f. d. ges. Anat. **86**: 698, 1928.
7. Warrington, W. R.: Personal communication.
8. Morley, J.: Abdominal pain, 1931, Wm. Wood & Co., New York.
9. Bank, J., and Cheskin, L. J.: Hepatitis as observed in an Army general hospital, Gastroenterology **6**: 357 (May) 1946.
10. Lichtman, S. S.: Diseases of the liver, gallbladder and bile ducts, 1949, Lea & Febiger, Philadelphia.
11. Flood, C. A., Seegal, D., Spock, B., and Loeb, R. F.: The differential diagnosis of jaundice, Am. J. M. Sc. **185**: 358, 1933.
12. Lindert, M. C. F.: Diagnosis in chronic liver disease, Wisconsin M. J. **49**: 769 (Sept.) 1950.
13. Barker, M. H., Capps, R. B., and Allen, F. W.: Acute infectious hepatitis in the Mediterranean Theater, J. A. M. A. **128**: 997 (Aug. 4) 1945.
14. Ottenberg, R., and Colp, R.: Diagnosis of surgical jaundice, New York State J. Med. 37: 1011, 1937.
15. Menof, P.: Infective hepatitis, South African M. J. **23**: 544, 1949.
16. Salvesen, H. A., and Lödöen, O.: Clinical studies on malignant hepatitis, Acta med. Scandinav. **137**: 305 (March 30) 1950.
17. Alsted, G.: Studies on malignant hepatitis, Am. J. M. Sc. **213**: 257 (March) 1947.
18. Havens, W. P., Jr., and Ginder, D. R.: The sequelae of virus hepatitis, Stanford M. Bull. **6**: 311 (May) 1948.
19. Caravati, C. M.: Posthepatitis syndrome, South. M. J. **37**: 251 (May) 1944.
20. Sherlock, S., and Walshe, V.: The posthepatitis syndrome, Lancet **2**: 482, 1946.
21. Barker, M. H., Capps, R. B., and Allen, F. W.: Chronic hepatitis in the Mediterranean Theater, J. A. M. A. **129**: 653, 1945.
22. Capps, R. B.: The differential diagnosis of jaundice, Rev. Gastroenterol. **16**: 117, 1949.
23. Bradley, S. E.: Variations in hepatic blood flow in man during health and disease, New England J. Med. **240**: 456, 1949.
24. Himsworth, H. P.: The liver and its diseases, 1947, Harvard University Press, Cambridge, Mass.
25. Nissen, H. A.: Cirrhosis of the liver showing jaundice and ascites, M. Clin. North America **4**: 555–569 (Sept.) 1920.
26. Snell, A. M.: Clinical aspects of portal cirrhosis, Ann. Int. Med. **5**: 338, 1931.
27. Chapman, C. B., Snell, A. M., and Rowntree, L. G.: Compensated cirrhosis of the liver, J. A. M. A. **100**: 1735, 1933.
28. Ratnoff, O. D., and Patek, A. J., Jr.: The natural history of Laennec's cirrhosis of the liver, Medicine **21**: 207, 1942.
29. Henrikson, E. C.: Cirrhosis of the liver, Arch. Surg. **32**: 413, 1936.
30. Hughson, W.: Portal cirrhosis with ascites and its surgical treatment, Arch. Surg. **15**: 418, 1927.

31. Means, J. H.: Case records of the Massachusetts General Hospital, New England J. Med. **232**: 87, 1945.
32. Watson, C. J., and Hoffbauer, F. W.: The problem of prolonged hepatitis with particular reference to the cholangiolitic type and to the development of cholangiolitic cirrhosis of the liver, Ann. Int. Med. **25**: 195, 1946.
33. Wilbur, D. L., Wood, D. A., and Willett, F. M.: Primary carcinoma of the liver, Ann. Int. Med. **20**: 453, 1944.
34. Hoyne, R. M., and Kernohan, J. W.: Primary carcinoma of the liver, Arch. Int. Med. **79**: 532, 1947.
35. Warvi, W. N.: Primary tumors of the liver, Surg., Gynec. and Obst. **80**: 643, 1945.
36. Brick, I. B.: Primary malignancy of the liver, Am. Pract. **1**: 475, 1950.
37. Rosenberg, D. M. L., and Ochsner, A.: Primary carcinoma of the liver, Surgery **24**: 1036, 1948.
38. Gustafson, E. G.: An analysis of 62 cases of primary carcinoma of the liver based on 24,400 necropsies at Bellevue Hospital, Ann. Int. Med. **11**: 889, 1937.
39. Auerbach, O., and Trubowitz, S.: Primary carcinoma of the liver with extensive skeletal metastases and panmyelophthysis, Cancer **3**: 837, 1950.
40. Wellman, G. O.: Solitary pyogenic abscess of the liver, Illinois M. J. **93**: 327, 1948.
41. Soro, Y.: Pylephlebitis and liver abscesses due to appendicitis, J. Internat. Coll. Surgeons **11**: 464, 1948.
42. Ochsner, A., DeBakey, M., and Murray, S.: Pyogenic abscess of the liver, Am. J. Surg. **40**: 292, 1938.
43. Rothenberg, R. E., and Linder, W.: The single pyogenic liver abscess, Surg., Gynec. and Obst. **59**: 31, 1934.
44. Dixon, C. F., and Murphy, G. T.: Primary idiopathic abscess of the liver, Surg., Gynec. and Obst. **54**: 20, 1932.
45. Drake, E. H., and Warthin, T. A.: Amebic abscess of the liver; therapeutic problems in various types of late hepatic amebiasis, New England J. Med. **239**: 45, 1948.
46. Ochsner, A., and DeBakey, M.: Amebic hepatitis and hepatic abscess, Surgery **13**: 460, 1943.

SOME SOCIAL IMPLICATIONS OF MEDICAL PROGRESS *

By Frank G. Dickinson, Ph.D., *Chicago, Illinois*

Introduction

When I received the invitation from President Middleton several months ago to give this paper, I was congratulated by several of my physician friends. I consider this opportunity to address you as a very real honor. Accordingly, I have tried to prepare something more philosophic than statistical. It will also be obvious that I am speaking to you as a social scientist, and that the views which I express are my own and not necessarily those of the American Medical Association.

Medical Progress Since 1900

I can remember the days when diphtheria was the scourge of childhood, when the red quarantine sign was a common sight on the doors along the streets of our little town in Western Illinois. I remember that my mother and grandmother would not allow the word "diphtheria" to be spoken above a whisper in the house, as if the very mention of it might bring down upon its speaker the awful curse of the disease. And I remember the little hearses made especially for children. They were often white, and some of them bore white plumes or were drawn by white horses as further designation that the departed was a child. Although time dims one's memories, enough of my childhood playmates died to leave a lasting, but hazy, imprint upon my memory of their tousled heads and blue eyes. It is little wonder that I should have these memories when I think of the fly-infested kitchens, the dead animals in the streets, the wash-tub baths once a week, the little outhouses.

Comparatively, there was little the physician could do. He was loved as he seldom is today, but in many ways he was powerless. His was almost a physical battle with disease. If a child survived birth, and often he did not, the raw milk he was fed might lead to fatal diarrhea. Too often babies did not live to run—even to walk. Of every thousand born in 1900, at least 150 did not reach their first birthday. Infant deaths accounted for one-fifth of the total number dying in 1900, but for only one-twelfth of the deaths in 1948. Even if a child survived the critical first year in 1900, he faced the "Big Four" of childhood diseases: scarlet fever, whooping cough, measles and dread diphtheria. And there were others—smallpox, mumps,

* Presented at the Thirty-second Annual Session of the American College of Physicians, St. Louis, Mo., April 13, 1951.

From the Bureau of Medical Economic Research of the American Medical Association.

and the still unconquered rheumatic fever and poliomyelitis. The common attitude among mothers of the day was "so many diseases over and so many still to go." Lockjaw, a rarity today, was an ever-present fear when a boy ran barefoot over the dirt roads and the fields, often stepping on a rusty nail or a loose piece of barbed wire. All a mother could do was wash out the wound, perhaps pour camphor into it, and wrap it with clean rags. Then she waited and prayed.

Even after all these dangers had been endured, youth faced an adulthood threatened by pneumonia, influenza or tuberculosis. It is difficult for young people today, with drugs and other treatment so readily available, to realize the horror these diseases wrought but a generation or two ago. In 1900, pneumonia, with or without the complication of influenza, was the leading killer in the United States, and even as late as 1918 an epidemic of "flu" and pneumonia swept through the country—the world—wiping out whole families as the Black Plague had done in Europe in the Middle Ages. "Consumption," or tuberculosis, was called the "White Plague," a term which seems overly dramatic today, for we see tuberculosis cured or arrested in case after case. But in 1900 diagnosis of "consumption" by a physician was the seal on a death warrant. By 1908 this disease had even replaced the pneumonia-influenza combination as the leading killer. Neither of these heads the list today, however. Progress against them, coupled with the decline of childhood diseases, has allowed heart disease and cancer to become the leading causes of death. In some parts of the world—for example, China—these latter diseases are not major medical problems because most of the people do not live long enough.

Today in the United States many of those who, under the medical knowledge and skill of 1900, would have died at birth or in their early years, are living on to old age because of health progress. The average number of life years gained can be computed, although the contributions to our culture made by these survivors cannot. The little hearse is gone. Perhaps it would have disappeared anyway with the advent of the motorized hearse. Relatively few children die today, or young people, either, except in accidents. In 1900 only four of a dozen funerals were for persons who had lived 50 years or more; in 1950, nine of a dozen funerals. Said another way, in 1900 the older half of the people dying had lived 30 or more years, the median age at death; in 1950, 66 or more years. The oldest three-fourths of the people dying in 1900 had lived two years or more, in 1948, 49 years or more. (One-fourth in 1900 had lived 62 years or more; in 1948, 76 years or more. The mean age rose from 34 to 59 years.) Life expectancy at birth rose from 49 to about 69 years now. These babies' mothers also have a better chance. Even as late as 1933, when the whole nation was included in the official registration area for the first time, the *lowest* mortality among the states was 4.3 deaths per 1,000 live births. By 1949 the *highest* rate among the states was only 2.4. Medical progress,

aided by better food, better housing, better sanitation, has been general throughout all sections of the United States.

But I needn't tell *you* about medical progress. One of the most significant facts which I would like you to remember is that, while the entire population of the United States has doubled since 1900, from 75 to 150 million, the population 65 and over has quadrupled, from three to 12 million. Health progress is the major reason for the latter, as the increased number of old is made up of those who would formerly have died in infancy and childhood. If our health conditions in 1950 had been the same as in 1900, twice as many persons would have died last year; that is, 1,600,000 more would have died.

The "Dying Man" of 1900 and of 1950

I have already mentioned that the median age at death in 1900 was 30, while in 1950 it was 66. Think of the difference—the difference between dying at 30 and dying at 66! It is the difference between being cheated of life and having the best of it. At 30 the "dying man" of 1900 was just getting established. His farm was probably still mortgaged, his children small. To his family, his death was more than personal loss: it was the loss of their means of livelihood. It is doubtful that the bitterness in his wife's heart was silenced either by fear of God, or love of God, or by the minister's funeral sermon on the impotence of man in the face of disaster and the acceptance of Divine Will.

Our "dying man" of 1950 leaves behind grown children already established in their own work and with families of their own. The widow probably has some income assured and, in an emergency, her grown children can help her. In spite of her grief, she must surely give thanks for all the years she and her husband had together, thanks that he lived to fulfill the goals of his youth, to see his home established, his children married and most of his grandchildren beyond infancy. Only the retired years have been denied him. Even this man's funeral sermon has been altered by the length of time he lived. The sermon is no longer filled with commands for acceptance of God's Will. Reminders of years of peace and accomplishment flow through it, assuaging the grief of relatives and friends as it never could at the death of a young man. Because so many more die old today, the bitterness of death for the survivors has been lessened.

Three Changes

What does this longer life mean to us today? Much as we rejoice as individuals, as members of society we must recognize that it is not an unmixed blessing. It has, in fact, made three very important changes in our culture today. Being an economist I would like to consider the economic change first.

1. *Crisis in Social Morality.* In 1900 we were a rural nation. The man who did live into the later years solved his problems of decreasing energy by merely cultivating a few less acres, reducing his work to caring only for his own needs, or supervising the younger farm hands. If he took a bit longer with the spring plowing, there was no one to object. Two-thirds of those over 65 continued to work. But today, in an industrial era, the aging and slowing worker is—justly or not—being forced out of his job to make room for a younger, faster worker. Many of these aging workers do not accept retirement willingly. These increasing numbers of old, unemployed persons present a serious economic and social problem. Retired on small private pensions and social security benefits which provide a lower standard of living than that to which they were accustomed, left with little to do and often treated as useless by society, many of them become frustrated. As their changed position in society seems to stem from lost earning power, many of them assume that with increased retirement income their position will revert to that of earlier days. Through unions and organized pressure groups, they are already making greater pension demands. You have merely to recall the number of articles on pension demands and social security legislation which have appeared in recent years to realize the extent of this problem.

In 1900 cradle-to-the-grave schemes could not have been successfully promoted. There were not enough old people. Today 35 per cent of our eligible voters have lived at least half a century, and a generation hence at least 42 per cent will be 50 years of age or over. These aged will have the power to form a political bloc capable of making economic demands upon society which could lead to national bankruptcy or a revolt of tax-burdened youth. The question we who are over 50 must ask ourselves today is, "How much do we want to exploit youth?" What standard of social morality should guide us? Do we want to fasten ourselves on the pay-checks of youth and ride piggy-back, or piggy-bank, to the grave? A generation ago, when I became old enough to vote, I could look forward to a lifetime of working, earning and saving. My children and your children face a future of working, earning and paying taxes. Is that fair?

Many ways of smoothing the path to retirement have been suggested. Some would postpone the retirement of capable workers and provide part-time or less exacting jobs for others. Some people feel that economic goals can be made less important to the aged by alleviation of social frustrations. Movies, radio and television programs, and church and community affairs directed toward the interests of the older segment of our population may help. Classes and clubs to develop wider interests and hobbies, and especially to stimulate creative activities which will replace job satisfaction, also seem promising. More rest homes, home nurses and housekeepers, and low cost or low rent housing, especially designed for safety and easy maintenance by the old, will be advocated. But the change considered

by many the most important is the alteration of society's attitude that the old are so many worthless beings whose opinions, even very existence, should be ignored as completely as possible. The aged must be granted a vital place in society again. It is perhaps, then, not too much to say that our aged population is the real "health crisis" of today.

2. *The Doctor's Dilemma.* For you, as physicians, this longer life brought about by medical progress has a second and ironic result. I have said already that in 1900 there was comparatively little the doctor could do, and yet that he was loved as he seldom is today. It was no accident that these two facts existed side by side. There, by the bedside of the dying child, hopeless and yet there, he stayed until he could do no more. When the child died, the parents consoled the doctor even as he consoled them. They had seen his tired face, hour after hour. They *felt* as well as knew that he had done his best. In so many cases today the doctor gives the sick child a shot of penicillin or other drugs, and then leaves to make other calls. Only after the doctor has gone does the miracle of the child's rallying occur. And though the parents' joy knows no bounds, and though their respect for, even awe of, the doctor is almost overwhelming, they are not drawn close to him. Often he remains impersonal—a technician, not a friend and counselor. He has not shared the bond. And strong as are the bonds of shared joy, even stronger are the bonds of shared sorrow.

Other factors, of course, have contributed to this change in attitude. Where formerly home visits were the rule, today the doctor sees patients in his office and in the hospital—far more formal and professional places of meeting. Preliminaries such as blood tests and roentgen-rays may be performed by auxiliary personnel to save the doctor time. Again, he is drawn further and further from the intimate relationship of yore. This loss has also been brought about by his success in another way. The real frontier left to the doctor today is the saving of old men and women—far less dramatic than saving babies.

In 1900 the practice of medicine was largely an art. There was still so little knowledge of so many diseases that the doctor went ahead almost blindly—hoping. Today he has good reason to expect most patients to respond to his treatment. It is largely in the diseases of age that the doctor must still rely on "art." And with every new medical discovery his practice becomes more "science" and less "art." How ironic that as the physician moves toward success in the practice of his profession he becomes further removed from the hearts of his patients!

The very respect which the physician has gained is endangered. Medical progress has been so rapid that today we have come to believe that if only we had had another doctor, another hospital, or money for more extensive tests, Aunt Emma need not have died. As the number of old clutching at the hope of yet a little longer life increases, so will the pressure to provide longer life. As children we laughed at the naïveté of Ponce de Leon who

searched for the Fountain of Youth. Yet, today we ourselves have come to believe in a Fountain of Youth in the guise of medical progress. We point to the miracles wrought by the wonder drugs and by phenomenal feats of surgery; they induce us to believe that tomorrow, or the day after, scientific research will surely be able to save us from a specific cause of death.

The physician cannot fulfill these hopes. If the desire for better health and longer life were not a fundamental drive in man, we might think that we have already reached the promised land. But medical progress will be inadequate as long as pain comes too often and death comes too soon. For man is still mortal, although medical progress has almost made him forget it. To the family of a dying man there is no adequate medical care. We can get enough bread, enough rest, enough excitement at any one time; but we cannot get enough of life. John Ruskin put it so simply: "There is no wealth but life." The doctor can save few accident victims who are dying even as they are reached. Yet because he cannot perform miracles, the doctor has been attacked as not fulfilling his duties. The increases in deaths from heart disease and cancer are pointed to as evidence of his failure. The public does not consider that the deaths due to these older diseases are as different from deaths due to other diseases as a worn-out tire is different from a blown-out tire. The physician is forever denied an ultimate triumph. If his patient does not die today, he will die in 20 years, or 30. But the frustrated public, refusing to recognize this, demands legislation which will *make* the physician provide the Fountain of Youth.

3. *The Preacher's Dilemma.* The third cultural change wrought by medical progress is primarily religious. Even as the physician has been toppled from his pedestal, the other highly educated man of 1900—the preacher—has also been knocked from his pedestal as a result of medical progress, *not* as a result of more education. Today the physician and the preacher face much the same dilemma. In 1900 the religion was still largely the religion of fear of death and fear of a vengeful God. A common theme was that from the PROVERBS:

"The fear of God is the beginning of wisdom."

The sermons of the day were full of references to burning through eternity in the flames of Hell for one's sins. The very hope of one's worthiness to attain Heaven was an indication of the deadly sin of Pride. Torn by the fear of death and the fear of punishment which would follow, the sinner's only hope was to throw himself upon the mercy of that Absolute Ruler Who had created him.

As disease after disease was conquered and man lived longer and longer, a great change began to take place in the minds of laymen and in the sermons of preachers. The clergyman began to depend less and less upon hellfire and damnation to sway his flock. The change that came about in his ser-

mons undoubtedly resulted from a growing sense that culture was changing, rather than from a cold analysis—such as the mortality changes provide—of what would move his listeners to goodness. Hope for the life to come became diminished by the fulfillment of the hope for a longer life, and the fear of meeting one's Creator was lulled with the lulling of the fear of death itself. Escape from diphtheria became possible, escape from tuberculosis, escape from death in childbirth.

The great exception has been escape from accidents. The main fear of death left in children today is the fear of death by violence. They are warned in crossing streets to watch out for cars. But except for a fatal accident to a playmate or a pet, or the death of a pet from natural causes, the horror of death is seldom brought home to children. The atomic age may greatly increase the fear of death by violence.

Today the median age at death has mounted to 66. A man seldom feels it necessary to cap any statement about "when I reach 60 . . ." with the humble ". . . God willing!" A man of today looks forward confidently to paying for his home, watching his children grow and marry, and retiring at last for a few years of leisure in which to watch his grandchildren grow to maturity. As death in many forms has been pushed back, the revenge of the Maker has become an almost empty threat, easily given but seldom fulfilled. It is like that of the unwise parent who each time puts off punishment of a child with, "*Next* time you do that . . .!" At last the threat becomes ignored, or even scorned. So it has become in religion. Disease cannot be taken seriously as an instrument of the Almighty when next week it may be conquered by a man with a microscope. Indeed, the conquest of disease has been brought about so often that man has gradually come to hold the subconscious belief that perhaps tomorrow or the day after medicine will be able to save him from death entirely. Only the diseases of age stand sullenly defiant, and the death of one's parents is somehow less tragic than the death of one's children. They have had their lives. It is only as a man approaches age and the shadow of death comes nearer and nearer that he begins to fear his God, and to wonder if he is worthy of meeting Him. Fear of the onset of a last illness also contributes to this late feeling for religion. One is never ready for that last illness to start or that last accident to occur, although later on, when recovery seems hopeless, he may welcome death. Perhaps that is why one finds so many older persons in our church congregations today. It is they who seek the ultimate meanings, the ultimate values; for them, earthly meanings and material values are fading.

Many other factors have indirectly contributed to the seeming decline of religion. (I am resisting the temptation to discuss the statistics on church membership and attendance.) One of the most prominent factors is the increased accumulation of worldly goods and real income which longer life and technologic advances have made possible. With this increased opportunity to realize materialistic goals formerly unattainable for most, the too

common goal of the American housewife has become "keeping up with the Joneses." Increases in real incomes have also brought other forms of entertainment which draw the congregation away from mid-week and Sunday evening services. At the turn of the century the church supper, the Sunday sermon and the Wednesday evening choir practice were the big events in the calendar, but these became "tame" as new amusements developed which did not force people to examine themselves for flaws of character. Freed of much of their fear of death by medical progress, they turned with relief to other forms of interest. With the usual wide sweep of the pendulum, the reaction against the narrowness of the Victorian era of nicety was so vast that religion suffered a blow from which it has not yet recovered.

Fear of God cannot be artificially instilled in man, and so long as medical progress continues, the fear of death which has helped to inspire fear of God will continue to decline. Does this mean the end of religion? I do not believe that is the only possible outcome of this dilemma. Fear is not the sole basis for religion. Even where there is knowledge, faith has a place; what is knowable is unlimited but where knowledge ends, faith must begin. Placed on a planet whirling through space—alone—man needs to be sure that he belongs. The persisting need over all the centuries, among all cultures, has been the need for a haven, for a feeling of belonging to something or someone who will shelter man in his times of sorrow and of death. It is a need to be sure of the importance of self. If religion is revived as a more active force in the lives of the American people, the implications of health progress must be recognized. I believe that there can be and should be a rebirth of religious faith.

Whatever may be the full effects of longer life upon religious faith, it can be said that reverence for life is the crowning feature of our American civilization. We do place a very high value on lengthening of life. It is the apex of our culture. When I sat on the green benches at St. Petersburg, Florida, four weeks ago tomorrow, and visited with the retired people who were enjoying the sunshine, I was troubled again by the philosophic question: "Has medical progress been too slow or too rapid during the Twentieth Century?" Medical progress can never be rapid enough for me, my wife, our children, their spouses and our grandchildren. But any social scientist might question if it is a good thing for our population to age so rapidly in so few decades, for so many to die old rather than die young. I raise my question about the rapidity of medical progress but I cannot answer my own question. It could be answered fully only by one who was at once the most profound of philosophers, the most inspired of clergymen, the wisest of physicians. Or I might state the corollary: "Why can't our standards of social morality and our social institutions keep pace with health progress?" I can only insist that this question, however it is phrased, is one of the most important of our time.

Conclusions

I realize that this has been more of a sketch than a speech, for no one of these three social implications of medical progress has been adequately covered. It may seem to you, too, that this sketch is a gloomy one; I do not mean to make it so. Despite the seeming disadvantages for our society created by medical progress, I want to see that progress continue, and I believe it will. However, by analyzing these problems or disadvantages, we shall be better able to solve them, and solve them we must.

First, we must raise our standards of social morality by considering the effects that old age security measures and all other laws would have upon youth. The young must not be exploited.

Second, we must realize that the threat of socialized medicine results, in part, from medical progress and the consequent aging of our population.

Third, as the fear of death and of God declines, we must not let religion degenerate into a moral philosophy—albeit an excellent moral philosophy—concerned with an extreme emphasis upon "the here and the now"; rather, we must again have an age of faith for people of all ages. Thereby we may once more gain the feeling that we belong.

Because you, as physicians, have had so large a rôle in the health progress that has changed our culture by lessening the fear of death and of God, a challenge has been given you, a challenge to understand and take an active part in studying the problems which health progress has brought to society. As I see it, the physician and the clergyman face substantially the same dilemma, and their dilemma is a product of the greatest cultural change of the Twentieth Century—perhaps of twenty centuries.

CASE REPORTS

SARCOIDOSIS WITH FATAL CARDIAC INVOLVEMENT*

By George C. Adickes, M.D., S. L. Zimmerman, M.D., F.A.C.P., and Edward S. Cardwell, Jr., M.D., *Columbia, South Carolina*

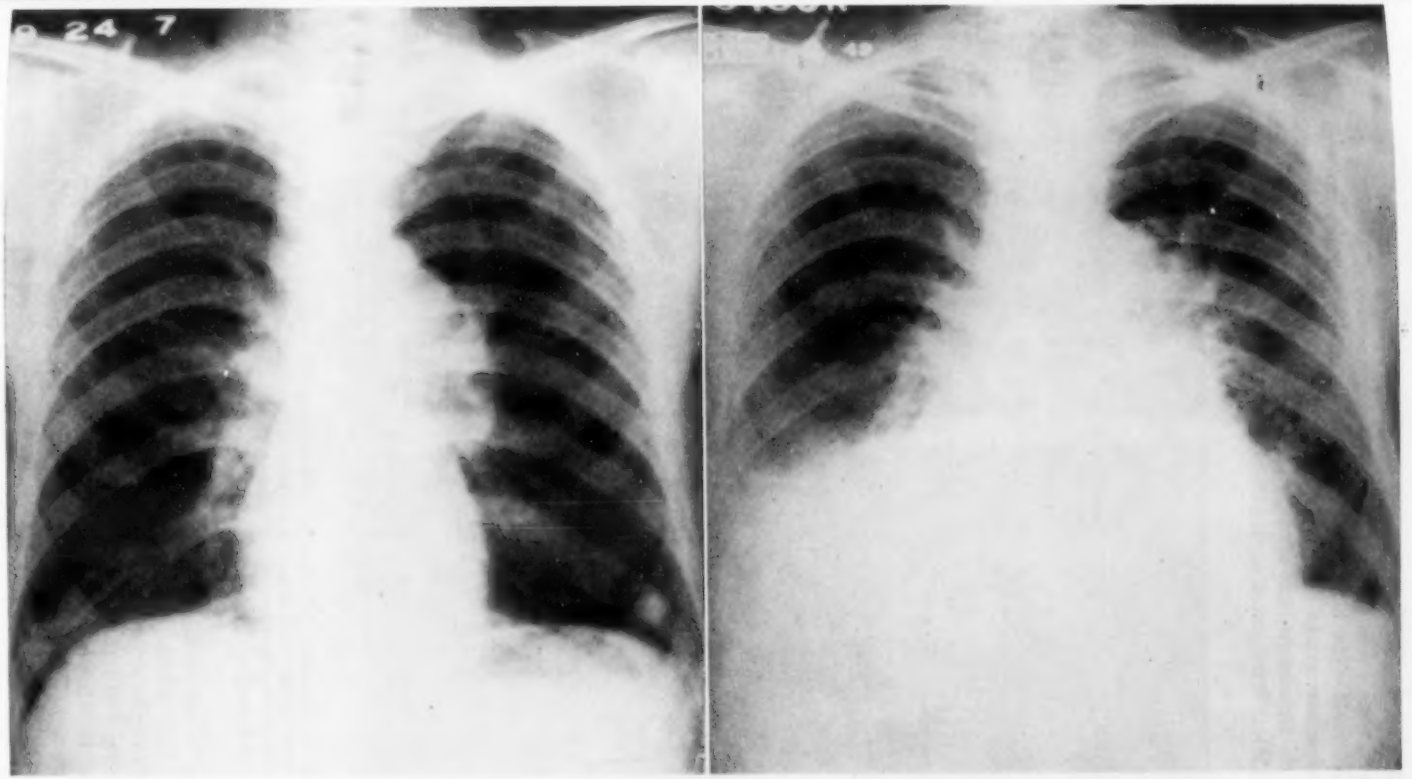
Scotti and McKeown [1] in 1948 reviewed the 12 recorded cases of sarcoidosis with cardiac involvement confirmed by necropsy and added one case of their own. Other cases of sarcoidosis presenting cardiac symptomatology but not verified by necropsy have been reported but are not within the scope of this paper. Freiman [2] states that cardiac lesions occur in a fair percentage of cases of sarcoidosis but that serious complications leading to cardiac symptomatology are rare. Many cases no doubt show cardiac effects as a result of chronic cor pulmonale secondary to pulmonary sarcoidosis.[3, 4] In Scotti and McKeown's review, only three cases displayed cardiac symptomatology which could be attributed directly to involvement of the heart; two additional cases had dyspnea which might be explained by pulmonary involvement with cor pulmonale, and there were three additional cases of sudden death showing sarcoid involvement of the heart at necropsy. Therefore, six of the 13 cases showing cardiac sarcoid lesions died as a result of their cardiac lesion. Two of this group presented clinical symptomatology of progressive myocardial failure, and one of these, reported by Johnson and Jason [5] and included in Scotti and McKeown's review, simulated very closely the case we are presenting now. Since Scotti and McKeown's review, Bates and Walsh [6] have reported a case of sudden death in a 32 year old Negro male who, at necropsy, showed sarcoid involvement of the heart.

Because of the relative rarity of progressive cardiac failure and arrhythmia culminating in death and caused by sarcoidosis, we feel this case worthy of reporting.

Case Report

A 28 year old Negro male saw mill laborer was admitted January 1, 1949, complaining of pain in the right upper quadrant, nausea and vomiting. He had been a patient in this hospital from September 23 to October 8, 1947, because of bilateral parotid gland enlargement of a month's duration. During that admission, chest roentgen-ray (figure 1A) revealed enlarged lymph nodes in the left hilar region, a normal heart and nodular infiltrations at the base of the right lung. A bilateral chronic anterior uveitis was found. Tuberculin skin test was negative. Roentgenograms of hands and feet showed no abnormalities; sputum examinations were negative

* Received for publication November 26, 1949.
From the Medical Service, Veterans Administration Hospital, Columbia, South Carolina, Dr. S. L. Zimmerman, former Chief. (Now Lt. Col., MC Reserve, Chief of the Medical Service, Murphy General Hospital, Waltham, Mass.) Sponsored by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are results of their own study and do not necessarily reflect the opinion or ruling of the Veterans Administration.

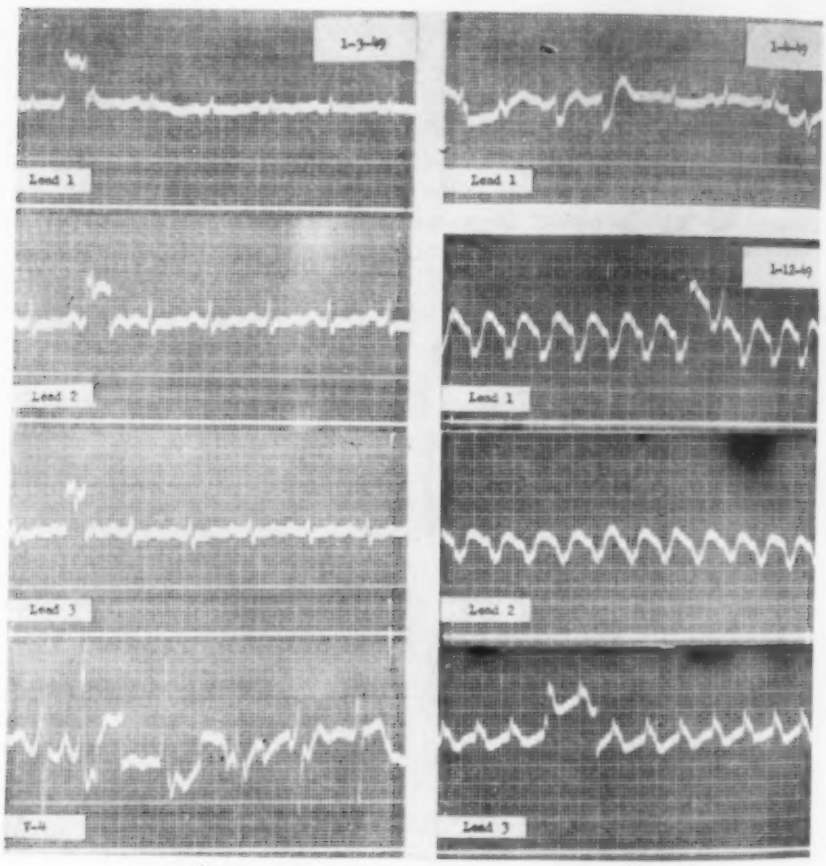


A B

FIG. 1A. Roentgen-ray on September 24, 1947, showing enlarged nodes in left hilar region, a normal cardiac silhouette and linear nodular infiltrations in right lower lung.

FIG. 1B. Roentgen-ray on January 4, 1949, showing enlarged nodes in left hilar region, an enlarged heart and a right-sided pleural effusion.

for acid-fast bacilli; blood count showed 11.5 gm. hemoglobin; sedimentation rate was 52 mm. per hour (Westergren). Total serum proteins were 5.61 gm., with an AG ratio of 1.3 to 1. The blood Kahn was 4 plus and blood Wassermann was 1 plus. There was a low grade fever (99° to 100° F.) throughout the hospital stay. A diagnosis of sarcoidosis was made. There were no available superficial glands for biopsy. Patient left against medical advice.



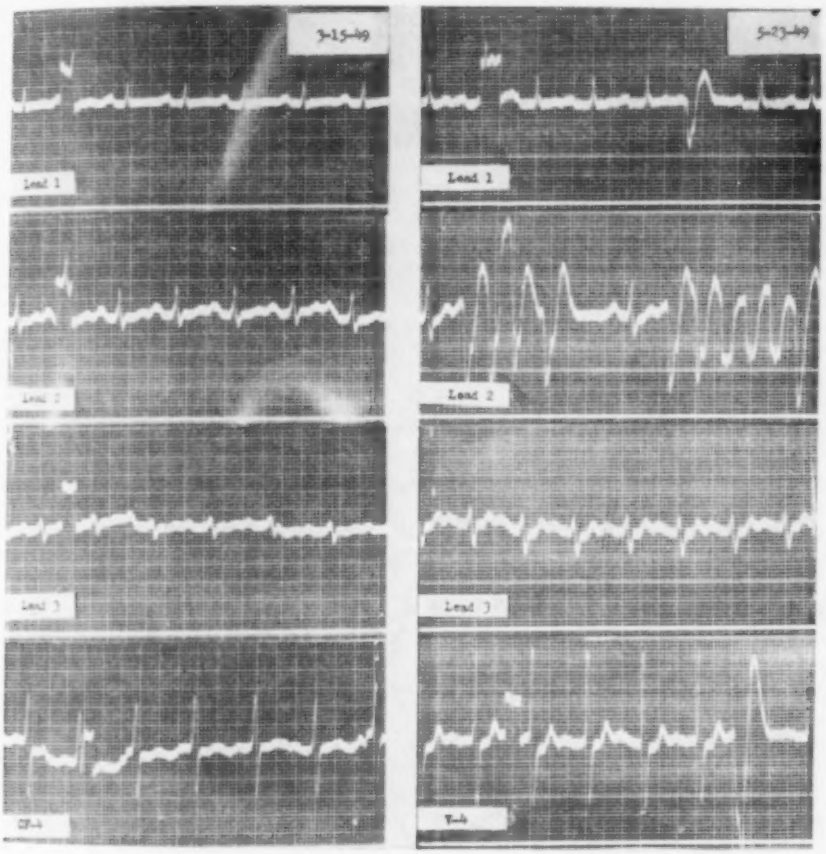
A B

FIG. 2. A. Sinoauricular rhythm with sagging ST segments, borderline low voltage and premature ventricular systoles, compatible with digitalis effect. B. Top tracing. Note multifocal origin of premature ventricular systoles. Tracing dated January 12, 1949 shows ventricular tachycardia.

Present acute episode began with nausea and vomiting about one week prior to admission. He had had pain in the right upper quadrant for about one year, which had been worse in recent weeks, and there had been frequent episodes of nausea and vomiting. He had returned to work after previous hospitalization, developed sudden shortness of breath while working six months before admission, and, because of exertional dyspnea, had been forced to stop work three months prior to admission. He had had occasional ankle edema which had become prominent in the past week and.

though he denied orthopnea, had been sleeping on two pillows. There had been a loss of about 10 pounds in weight despite the edema.

Past history revealed pneumonia at age 15, gonorrhea at age 10, moderate use of tobacco, liberal use of alcohol until three years before, when he stopped drinking, nocturia three to four times, frequent palpitation for several months, and a chronic, slightly productive cough for several years. There was no history of rheumatic fever or rheumatic equivalents.



A B

FIG. 3. A. Sinoauricular rhythm, first degree AV block, intraventricular conduction defect, probably a quinidine effect. B. Note recurrence of premature contractions of multifocal origin, indicating extreme myocardial irritability.

Physical examination on admission revealed a fairly well developed and nourished young colored male, 72 inches tall, weighing 156.5 pounds. The blood pressure was 90 mm. Hg systolic and 70 mm. diastolic; pulse, 84 per minute; respirations, 22 per minute, and temperature, 99.4° F. The sclerae were muddy. There was swelling of both sides of the face at the angles of the jaws, but no definite masses or glands could be outlined. The neck veins were distended; there was slight pitting edema of the ankles and pretibial regions. The percussion note was impaired over the right

lower chest posteriorly, with distant breath sounds and diminished fremitus in this region and occasional fine crepitant râles just above. The heart was enlarged to the left; there was no increase in mediastinal dullness; a harsh, grade 3 to 4 whistling systolic murmur was present over the apex. The rhythm was regular sinus and a gallop was noted, heard best in the third intercostal space just to the left of the sternum. P_2 was accentuated and louder than A_2. There was exquisite tenderness over the liver which extended 5 cm. below the right costal cage in the midclavicular line. Small, shotty, nontender axillary and right epitrochlear glands were palpable. The retinal vessels were normal in appearance and the peripheral vessels were soft. The physical examination was otherwise normal.

In considering the differential diagnosis at this time, the possibility of a rheumatic carditis or a nonspecific carditis of viral origin was entertained. However, because of the absence of a history of rheumatic fever or any joint involvement, and the absence of demonstrable pericardial or definite endocardial involvement, rheumatic fever as an etiologic factor was thought unlikely. A viral carditis could not be dismissed so readily, and subacute bacterial endocarditis could not be ruled out. There was no history of antecedent hypertension or coronary insufficiency; syphilis as a possible cause of congestive failure, not dependent upon aortic valvular disease, was considered because of his previous positive serology, but it is so rare it was virtually dismissed as an etiologic possibility. There was no evidence for such obscure etiologic factors as beriberi, thyrotoxic heart disease, pericardial constriction or tamponade; neither was there evidence of diffuse arterial or arteriolar disease to support the concepts of periarteritis nodosa or diffuse subendocardial fibrosis on a vascular basis. Because of other evidences of sarcoidosis, the patient was initially labeled as probable sarcoidosis involving the heart with congestive failure.

On admission, bed rest, low sodium diet and sedation were instituted and the patient was given 1 c.c. of a mercurial diuretic intramuscularly. On the second hospital day, because of a totally irregular rhythm thought to be auricular fibrillation clinically, he was rapidly digitalized. An electrocardiogram on the third hospital day (figure 2) showed a sinus rhythm, sagging ST junctions and inverted to diphasic T waves suggestive of digitalis, and borderline low voltage. On the fourth hospital day the venous pressure was measured at 22.6 cm. of saline, and later in the day, because of the recurrence of a grossly irregular rhythm, an electrocardiogram (figure 2) was obtained which showed an irritable myocardium, with numerous premature ventricular systoles arising from varied foci. Quinidine sulfate, in 3 gr. doses, was administered orally every three hours. The rhythm became regular, the rate normal. On the eleventh hospital day the dosage was reduced to gr. 3 every eight hours. Signs of congestive heart failure had meanwhile gradually subsided. The gallop over the right side of the heart persisted. On the twelfth hospital day, a tachycardia of approximately 180 per minute appeared and an electrocardiogram (figure 2) revealed a ventricular tachycardia. Digitalis was discontinued. Quinidine was increased to gr. 6 every two hours; after 24 hours the tachycardia subsided and quinidine was continued in dosages of gr. 3 every four hours. Because premature systoles appeared just prior to medication, the quinidine was increased to gr. 3 every three hours on the fifteenth day and, after a brief episode of ventricular tachycardia on the seventeenth day, to gr. 3 every two hours. Attempts to reduce the frequency and amount of quinidine were unsuccessful in that quinidine gr. 3 every three hours was required subsequently to maintain an effective heart rhythm (figure 3).

Laboratory data included an initial chest roentgen-ray (figure 1B), showing an enlarged heart, a small pleural effusion at the right base and a mass in the left hilar and para-aortic region, probably representing lymph nodes. Subsequent chest roentgen-rays showed clearing of the pleural effusion and some decrease in the size of the heart, as well as some increase in size of the lymph nodes; the nodular infiltrations

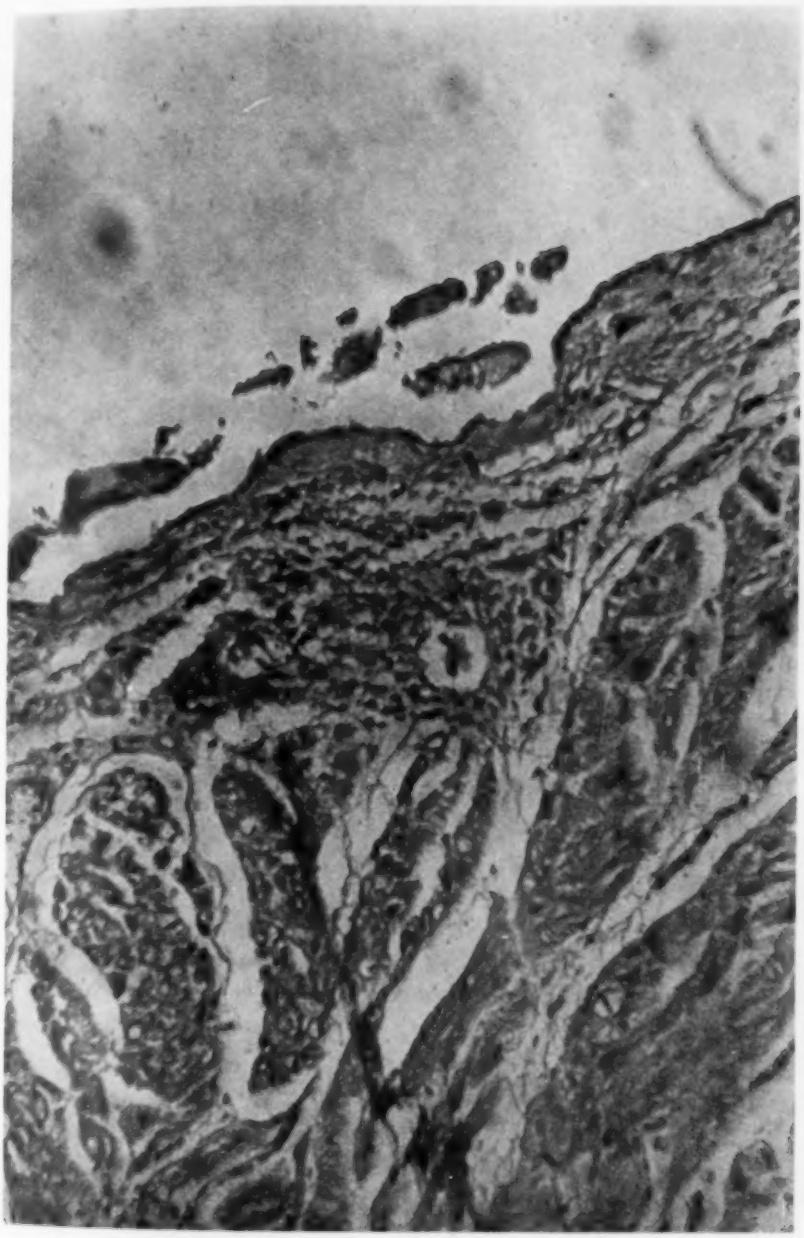


FIG. 4. Collection of epithelioid cells and lymphocytes (atypical tubercle) in pericardium of auricle. × 100.

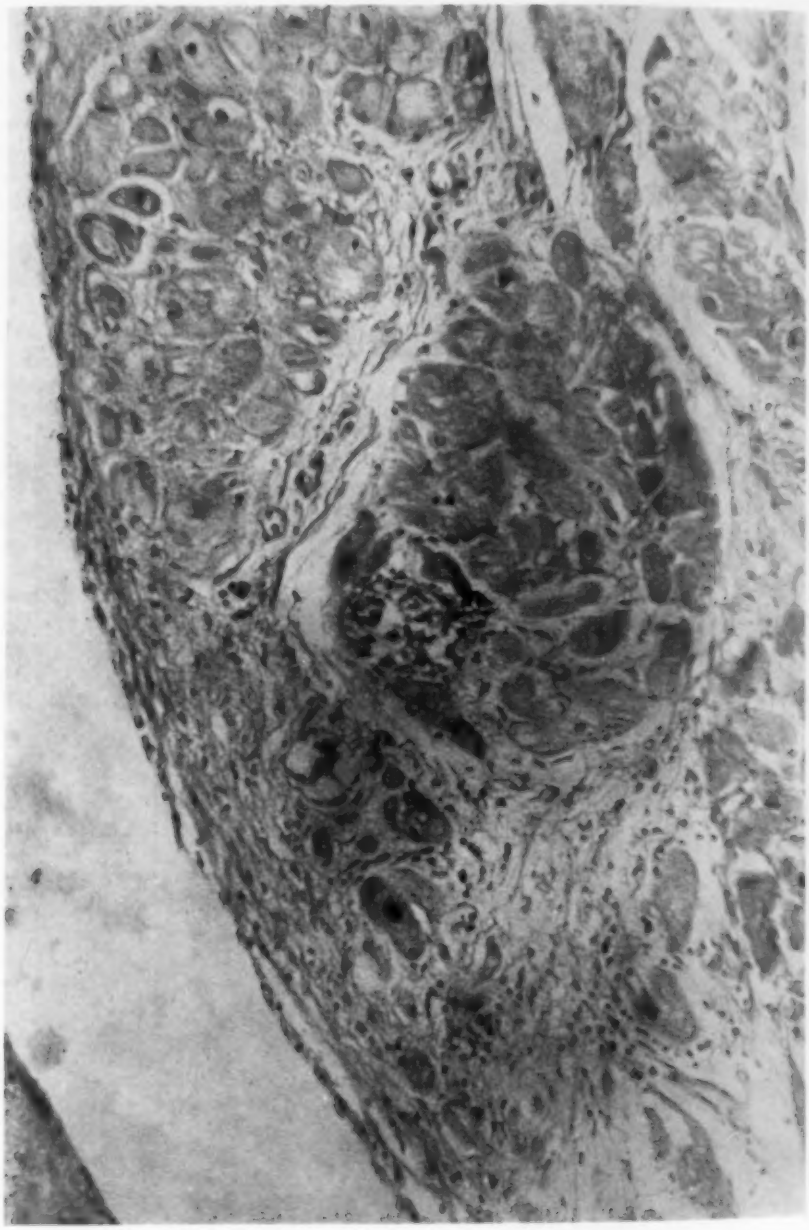


FIG. 5. Small collection of epithelioid cells in left ventricular musculature. Poorly developed giant cell in adjacent area to left and above. General recent fibrosis and slight infiltration by lymphocytes and mononuclear leukocytes. × 100.

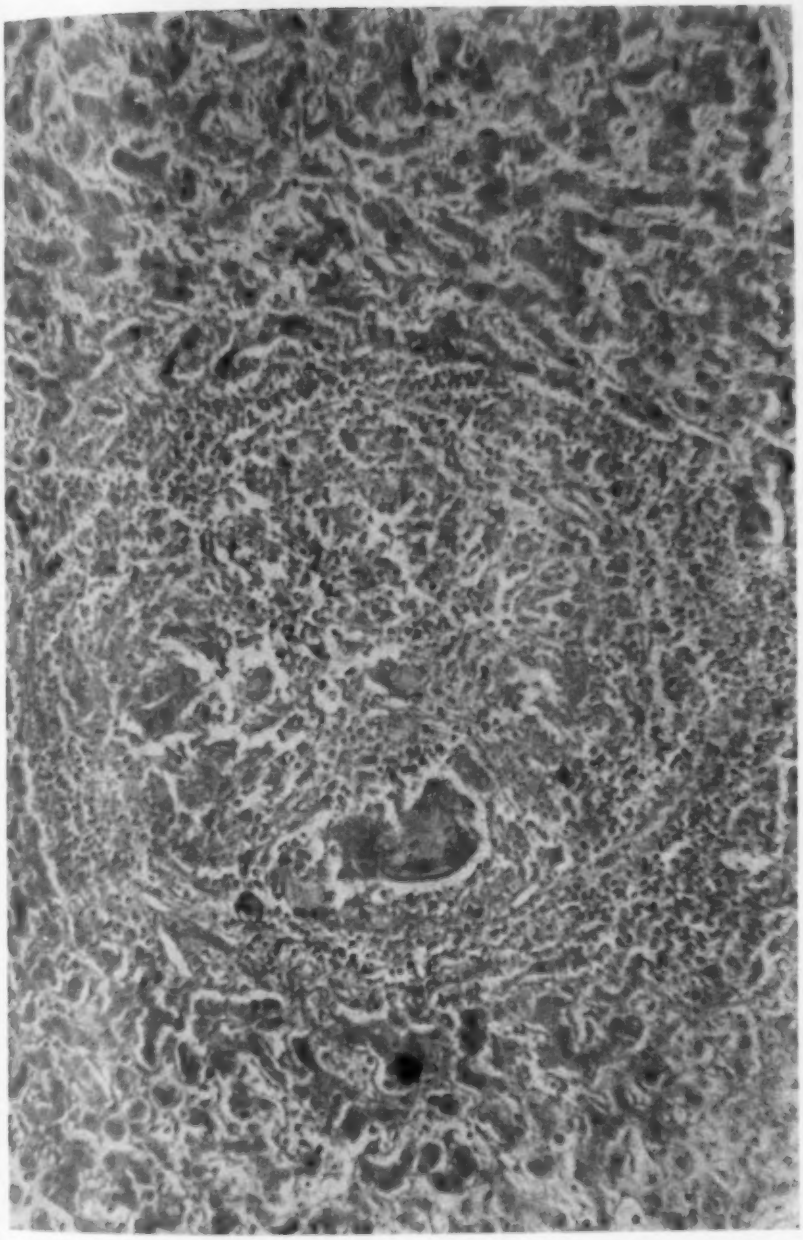


FIG. 6. Typical tubercle in liver. × 100.

FIG. 5. Small collection of epithelioid cells in left ventricular musculature. Poorly developed giant cell in adjacent area to left and above. General recent fibrosis and slight infiltration by lymphocytes and mononuclear leukocytes. × 100.

noticed in the right lung on the first admission could be seen after disappearance of the pleural effusion. Roentgenograms of the hands and feet were negative, showing no evidence of sarcoidosis. Numerous urinalyses showed good specific gravities, no albumin or sugar, and no cellular elements except occasional white blood cells. White blood counts varied from 3,800 to 7,800, with a mean of 5,600 (in the 25 counts during his hospitalization), and a mean of 51 per cent polymorphonuclear leukocytes; a mean of 13 gm. of hemoglobin; normal color and volume indices, a sedimentation rate varying from 0 to 26 mm. per hour (Wintrobe), and a hematocrit ranging from 34 to 50. Blood Kahn was negative. Total serum proteins on the fourth hospital day were 5.95 gm. per 100 c.c., with an AG ratio of 1.06:1, and during the third month of hospitalization were 6.72 gm., with an AG ratio of 1.06:1. Intradermal tuberculin skin tests were negative. Icterus index on the fourth hospital day was 13.9 units; cephalin cholesterol flocculation, 1 plus in 48 hours. Total quantitative serum bilirubin varied from 0.65 mg. to 1.9 mg. per 100 c.c. of serum; total serum cholesterol was 140 mg. per 100 c.c., with 73 mg. as esters; prothrombin time varied from 17 to 17.5 seconds (53 to 69 per cent of normal controls). Blood cultures were repeatedly negative.

During the third month of hospitalization, signs of congestive heart failure recurred but were satisfactorily controlled with the cautious administration of digitalis and mercurial diuretics, except that the patient frequently complained of epigastric pain, particularly when in the upright position, and that the liver remained somewhat enlarged and at times was tender. He remained afebrile throughout his hospitalization. The patient became suddenly dyspneic and died on June 26, 1949.

Autopsy

Autopsy was performed approximately three hours after death. The body was fairly well developed, weighing about 160 pounds and measuring 72 inches in length. Rigor mortis was well developed and generalized.

Peritoneal Cavity: No free fluid or adhesions.

Pleural Cavities: Empty; no adhesions.

Lungs: Left lung, 460 gm.; right lung, 450 gm. Both lungs were crepitant and air-bearing throughout, and no areas of consolidation or calcification were seen. In each apex there were several emphysematous blebs up to 1 cm. in diameter. A moderate amount of blood flowed from the cut surfaces, and a small amount of clear fluid could be expressed from the cut surfaces of the lower lobes.

Trachea and Bronchi: Contained a small amount of clear frothy fluid. The mucosal surfaces were not congested or ulcerated.

Pericardial Cavity: Contained about 50 c.c. of clear serous fluid. The pericardial surfaces were smooth and glistening.

Heart: Weight, 560 gm. Beneath the pericardium covering the wall of the left ventricle there was an ovoid "milk spot" measuring 2 by 3 cm. The myocardium was generally flabby. In the myocardium of the left ventricle there was an occasional minute white dot. The chambers were dilated and contained partly clotted blood. The endocardium was smooth and the valves were not abnormal. No plaques were seen in the aorta or coronary arteries. Measurements of the heart in centimeters were: left ventricle 2, at apex, 1; right ventricle, 0.5; left auricle, 0.2; right auricle, 0.2; tricuspid valve, 12; mitral valve, 10; pulmonary valve, 7; aortic valve, 6.

Liver: Weight, 1,540 gm. Consistency was as usual, and the capsule was smooth and glistening. The cut surface was clear and the vascular markings were slightly more prominent than usual. The gall-bladder was not abnormal.

Spleen: Weight, 180 gm. The capsule was smooth and glistening and consistency was considerably increased. The cut surface was dark purple and scraped fairly easily.

Adrenals: Nothing unusual.

Kidneys: Right, 150 gm.; left, 125 gm. Faint marks of fetal lobulation were present. Consistency was as usual. The cortex and medulla were proportionate and clear. There was nothing unusual seen in the pelves, ureters and bladder.

Esophagus, Stomach, Intestines and Pancreas: Nothing unusual.

Lymph Nodes: The tracheobronchial lymph nodes were enlarged to form a mass 9 cm. in diameter. The nodes were discrete and generally pale, gray and elastic. No areas of caseation were seen. The other lymph nodes were not enlarged.

The brain was not examined.

Microscopic:

Lung: The alveoli were generally large and some appeared to be confluent. The alveolar capillaries contained very little blood. In one section the alveoli were partly collapsed and contained a small amount of free blood. Scattered throughout the sections in the alveolar walls were several small collections of epithelioid cells. These varied considerably in size and shape but were generally rather small. There was very little lymphocytic infiltration, and no foreign body giant cells or caseation.

Tracheobronchial Lymph Nodes: Throughout the sections there were numerous small collections of epithelioid cells arranged in tubercle formation; some of the larger ones were confluent. There was an occasional foreign body giant cell. The tubercles were generally separated by a considerable amount of hyaline fibrous connective tissue in which there was slight lymphocytic infiltration. In one lymph node there was very pronounced scarring, and the tubercles here were less numerous. This change appeared to be limited to the lymph node, the adjacent tissues not being involved.

Heart: In a section taken from the left ventricle, the interstitial tissue generally was rather loose and appeared to be edematous. There was slight diffuse infiltration by lymphocytes and an occasional polymorphonuclear leukocyte. There was an occasional dense focus of these cells. Here there were a few large cells which had irregular nuclei and a large amount of eosinophilic cytoplasm. A few of these cells were multinucleated. There were numerous large areas of scar tissue. The myocardial fibers were generally large, this being most pronounced in the areas of scarring. In the section taken from one of the auricles there was a small collection of epithelioid cells in the subpericardial fibrous connective tissue. There were slight lymphocytic infiltration here and two giant cells of the foreign body type.

Aorta: Nothing unusual.

Liver: The liver cells were generally rather small and had a granular cloudy cytoplasm. Scattered throughout the liver there were numerous small collections of epithelioid cells surrounded by a few lymphocytes. Foreign body giant cells were fairly numerous, particularly in the largest tubercles. There was no caseation.

Spleen: Hyperplasia of the germinal follicles. Occasional tubercles similar to those in the liver. Foreign body giant cells were much less common here. Congestion.

Kidney: Cloudy swelling of the convoluted tubular epithelium. Irregular lymphocytic infiltration of the interstitial tissue. Congestion. Occasional small area of scarring in the outer part of the cortex. Albuminous casts in the tubules.

Acid-fast bacilli could not be demonstrated in any of the sections.

Final Autopsy Diagnoses: (1) Boeck's sarcoid of lungs, heart, tracheobronchial lymph nodes, liver and spleen; (2) hypertrophy of heart, left ventricular; (3) pyelonephritis, chronic; (4) emphysema, pulmonary, focal.

Discussion

This, then, is a case of chronic progressive myocardial failure, complicated by a frequently recurring arrhythmia consisting of multifocal ventricular premature

systoles with prolonged runs of ventricular tachycardia. The extreme myocardial irritability was controlled with varying doses of quinidine, dependence being placed upon larger doses at two hour intervals to control the bouts of ventricular tachycardia. Zimmerman [7] has previously reported on the beneficial effects of large doses of quinidine administered at frequent intervals in the control of ventricular tachycardia. The results with respect to this aspect of the case were gratifying. It is extremely doubtful in our minds that digitalis was etiologically related to arrhythmia, since the patient definitely exhibited a totally irregular rapid rhythm prior to the administration of the drug, and also because the ventricular tachycardia recurred at frequent intervals even after a period of withholding digitalis for as much as two weeks. However, because of the exacerbation of the signs and symptoms of congestive heart failure, even though the regimen was, in other respects, carried out along the lines of presently acceptable concepts, it became necessary to readminister the drug cautiously. The possibility of enhanced myocardial irritability as a result of digitalis was appreciated. The problem, then, was reduced to the administration of the minimal amount of digitalis which would improve the congestive failure and the exhibition of sufficient quinidine at seemingly proper intervals to lessen myocardial irritability or actually to control an already established ventricular tachycardia.

The differential diagnosis has been mentioned earlier in the paper. On admission, the various causes of cardiopathy with congestive failure were considered. The various etiologic factors were later reduced to three: Boeck's sarcoidosis, rheumatic carditis and nonspecific carditis of viral origin. It was impossible clinically to exclude any of the above, but the patient was listed as probable sarcoidosis of the heart, in view of the other manifestations of sarcoidosis, the absence of a rheumatic background, endocardial lesions, arthritis or pericardial involvement. Viral myocarditis could not be excluded on clinical grounds. In addition, we were anxious to make a diagnosis of Boeck's sarcoidosis of the heart in an individual with the syndrome who presented congestive failure of obscure origin. The clinical impression was confirmed at necropsy.

It is our impression that this is the first time a diagnosis of sarcoidosis of the heart with congestive heart failure was made clinically and confirmed at necropsy. Dr. Harry Price, of the Medical Service at Lawson Veterans Hospital, informs us that in a recent review of approximately 200 cases of sarcoidosis there was none with cardiac involvement. Dr. E. T. Odom, Chief of Medicine at the Tuskeegee Veterans Hospital, who previously had a relatively rich experience with sarcoid disease at the Meharry Medical School, and who has subsequently seen a fairly large number of cases, cannot recall one with clinically significant cardiac involvement. It is obvious, therefore, that the syndrome is rare.

We cannot hazard an explanation as to why the lesions of sarcoidosis were so typical in the lymph nodes, liver, spleen and elsewhere, and why they were so atypical, but nonetheless compatible with the diagnosis, in the myocardium. Here fibrosis, diffuse and extensive, was the predominant lesion. Scattered here and there were suggestively typical tubercles, not unlike those present elsewhere and pathognomonic of sarcoidosis. Epithelioid cells, lymphocytes and rare giant cells were seen. Numerous observers [8, 9, 10, 11, 12] stated that fibrosis may repre-

sent the late sequelae of sarcoidosis. The findings in the myocardium were not unlike those reported by Johnson and Jason [5] in their case report on cardiac sarcoidosis.

After a reasonably thorough perusal of the English literature one is struck by the relative rarity of cardiac deaths due to direct sarcoid involvement of the heart. The total number of reported cases of this type is small. The cases exhibiting clinical signs of progressive heart failure are even fewer in number.

Conclusions

1. A case of sarcoidosis with fatal cardiac involvement is reported.

2. The extreme rarity of the syndrome of progressive congestive heart failure due to cardiac sarcoidosis is stressed.

3. Boeck's sarcoidosis must be considered in the differential diagnosis of congestive heart failure of obscure etiology, especially if it occurs in a young Negro male.

4. Other evidence of sarcoidosis—in the lung parenchyma, the hilar or peripheral lymph nodes, the liver or spleen, the bones of the hands and feet, the uveal tract, the parotid gland and the skin—may be the clue that will aid in the correct differentiation.

BIBLIOGRAPHY

1. Scotti, T. M., and McKeown, C. E.: Sarcoidosis involving the heart; report of a case with sudden death, Arch. Path. **46**: 289, 1948.
2. Freiman, D. G.: Sarcoidosis, New England J. Med. **239**: 664, 1948.
3. Schaumann, J.: On nature of certain peculiar corpuscles present in tissue of lymphogranulomatosis benigna, Acta med. Scandinav. **106**: 239, 1941.
4. Hauser, H.: Pulmonary sarcoidosis, J. Oklahoma M.A. **39**: 395, 1946.
5. Johnson, J. B., and Jason, R. S.: Sarcoidosis of the heart; report of a case and review of the literature, Am. Heart J. **27**: 246, 1944.
6. Bates, G. S., and Walsh, J. M.: Boeck's sarcoid; observations on seven patients, one autopsy, Ann. Int. Med. **29**: 306, 1948.
7. Zimmerman, S. L.: Ventricular tachycardia; a report of ten cases, eight of which were treated with quinidine with recovery in seven, Ann. Int. Med. **23**: 634, 1945.
8. Longcope, W. T., and Pierson, J. W.: Boeck's sarcoid (sarcoidosis), Bull. Johns Hopkins Hosp. **60**: 223, 1937.
9. Hollister, W. F., and Harrell, G. T.: Generalized sarcoidosis of Boeck accompanied with tuberculosis and streptococcic bacteremia; clinicopathologic study with autopsy and animal inoculations, Arch. Path. **31**: 178, 1941.
10. Bernstein, S. S., and Oppenheimer, B. S.: Boeck's sarcoid; report of six cases with one necropsy, J. Mt. Sinai Hosp. **9**: 329, 1942.
11. Tice, F., and Sweany, H. C.: Fatal case of Besnier-Boeck-Schaumann's disease with autopsy findings, Ann. Int. Med. **15**: 597, 1941.
12. Pinner, M.: Pulmonary tuberculosis in the adult, 1945, Charles C Thomas, Springfield, Illinois, p. 342.

HYPOPROTHROMBINEMIA DUE TO DICUMAROL IN A MALINGERER: A CASE REPORT *

By William A. Stafne, M.D., F.A.C.P., and Allan E. Moe, M.D.,
Fargo, North Dakota

Since the isolation and synthesis of Dicumarol by Link and his co-workers in 1941, and its subsequent utilization in the prevention and treatment of thromboembolic phenomena, numerous articles have appeared in the literature emphasizing the need for caution in its administration to prevent serious consequences. The case to be presented is one of Dicumarol poisoning, a result of malingering, with widespread hemorrhages of serious import.

Case Report

The patient, a 26 year old graduate nurse, entered the hospital May 16, 1947, complaining of pain across the middle of her back of two days' duration. According to the patient, on the evening of admission the pain had become increasingly severe, with localization over the right lower dorsal region and radiation into the flank. There had been some frequency of urination, but no other abnormal signs or symptoms had been noted.

Past history and systemic review disclosed the following: appendectomy, 1935; pelvic laparotomy, 1941, at which time a right salpingectomy had been performed; dysmenorrhea of long standing, and bouts of lower abdominal pain associated with nausea and vomiting in 1944 and 1946. Repeated roentgenographic studies of the gall bladder, stomach and colon had been negative.

Physical examination revealed a well developed pale white female who seemed in much pain. The blood pressure was 124 mm. Hg systolic and 80 mm. diastolic; the pulse rate, 88 per minute; temperature, 100.2° F. The only significant finding was definite tenderness on pressure over the right costovertebral angle. A tentative diagnosis of right nephrolithiasis was entertained.

Emergency laboratory studies showed a hemoglobin level of 12.4 gm., red count 4,050,000, and a leukocyte count of 7,500. The urinalysis was normal except for 10 to 15 red blood cells per high power field. The following morning there were 30 to 100 red blood cells per high power field, and the leukocyte count remained unchanged.

Two days after admission, ecchymoses were noted at sites where the patient had received hypodermic injections for pain, and also in the antecubital spaces where blood had been drawn for laboratory procedures. Further examination revealed large ecchymotic areas over the buttocks, the site of penicillin injections during the previous two days, and several smaller ones over the thighs and legs. A tourniquet applied between systolic and diastolic blood pressure for five minutes to the upper part of the arm produced numerous petechiae in the antecubital space and forearm. The spleen and liver were not palpable. Detailed hematologic studies demonstrated a markedly prolonged bleeding time (the procedure was discontinued after 12 minutes); coagulation time (Lee-White method), 15 minutes; platelet count, 133,000; prothrombin time, 10 per cent of normal; blood urea nitrogen, 19.6 per 100 c.c. of blood; partial clot retraction after 24 hours, and blood calcium, 8 mg. per 100 c.c. of blood. Peripheral blood smears revealed normal morphology.

* Presented at the Regional Meeting of the American College of Physicians, Grand Forks, North Dakota, September 10, 1949.
Received for publication December 4, 1949.
From the Department of Internal Medicine, Fargo Clinic, Fargo, North Dakota.

The patient was immediately given a transfusion of fresh citrated blood, and daily administration of synthetic vitamin K was begun. By the fourth day the patient showed much subjective improvement, with a return to normal of the bleeding and coagulation time and platelet count. The prothrombin time rose successively to 21 per cent on the second day, 32 per cent on the fifth day, 50 per cent on the seventh day, 58 per cent on the ninth day, 71 per cent on the eleventh day, and 100 per cent on the nineteenth day. In retrospect it seems very likely that self-administration of Dicumarol was continued during part of this period.

Liver function studies, serum bilirubin and protein determinations were all interpreted as normal. Intravenous urogram was normal. When the patient was dismissed from the hospital, the urine revealed no blood cells, although gross blood had been noted on several previous occasions. No definite diagnosis had been made on dismissal after 19 hospital days. She was advised to take daily 1 mg. Synkamin orally, and during the next two weeks the prothrombin time remained within normal limits.

When she reported back July 3, 1947, the prothrombin time had fallen to 18 per cent of normal. She was placed on Synkamin intramuscularly, and the prothrombin time was checked daily for five days, with the following percentages reported: 18, 28, 30, 23 and 14. Liver function tests were repeated, with negative results.

As we were suspicious of self-administered Dicumarol, the patient was again hospitalized with the understanding that she was to undergo a period of study. Obviously the Dicumarol would have to be brought in by the patient if the prothrombin deficit was to persist. A search was made of the patient's belongings and her supply of the drug was found.

Previous attempts to elicit significant psychiatric information having met with failure, it was decided to discuss with the patient the possible consequences of self-medication and to confront her with the evidence. After affording her every opportunity to present the information, with no result, this was done. Even after this, the patient continued to deny self-medication and would not admit to any conflicts. No further attempt to elicit information was made, the patient being told merely that a recurrence of these symptoms would mean her dismissal from employment. She is still in the employ of the hospital as a very efficient supervisor. When she was hospitalized for an acute upper respiratory infection in the spring of 1949, all of the blood studies were normal.

We have not found a previously reported case of a malingerer's using Dicumarol. The motivating factors in this case are unknown to us.

Fatalities directly attributable to hemorrhage induced by Dicumarol are exceedingly rare in well followed cases.[1, 2, 3]

Physicians should consider this drug in the differential diagnosis of any disorder characterized by hemorrhagic manifestations for which no cause is apparent.

BIBLIOGRAPHY

1. Shleven, E. L., and Lederer, M.: Uncontrollable hemorrhage after Dicumarol therapy with autopsy findings, Ann. Int. Med. **21**: 332–342, 1944.
2. Rosenbloom, D., and Crane, J. J.: Massive hematuria due to Dicumarol overdosage, J. A. M. A. **132**: 924–925, 1946.
3. Barker, N. W., Cromer, H. E., Hurn, M., and Waugh, J. M.: Use of Dicumarol in prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration, Surgery **17**: 207–217, 1945.

ACUTE IDIOPATHIC HEMOLYTIC ANEMIA: REPORT OF A SEVERE FATAL CASE WITH IMMUNOLOGIC OBSERVATIONS *

By CHARLES G. CRADDOCK, JR., M.D.,† *Charlottesville, Virginia*

HEMOLYTIC destruction of red blood cells as a result of the activity of circulating agglutinins and hemolysins is often encountered clinically. The antigenic stimulus for the sudden appearance of these abnormal antibodies in various types of transfusion reactions is well understood and their presence is usually demonstrable by in vitro technics. In the case of idiopathic acquired hemolytic anemia, however, the immunologic processes are not understood. The classic work of Dameshek and Schwartz [1] leaves little doubt that the presence of hemolysins or agglutinins plays an important part in the pathologic destruction of red cells in these cases. Similar findings have been reported by numerous investigators. Since the discovery of blocking antibodies by Wiener [2] and Race [3] in 1944, particularly in regard to the Rh factor, technics have been developed which have permitted more frequent demonstration of the immunologic abnormalities in acquired hemolytic anemia.

The appearance of acquired hemolytic anemia in a completely normal individual without any apparent causative phenomena remains an entity of obscure origin. That sometimes the onset may be rapid and the clinical course stormy is well known. The case presented herewith represents one of severe degree with explosive onset, fulminating course and fatal termination. There is no doubt that this case belongs in that relatively rare group of anemias called acute idiopathic hemolytic anemia. The criteria necessary for the diagnosis, as set forth by Dameshek and Schwartz,[1] are fulfilled. Of interest is the fact that the abnormal antibodies presumed responsible for the massive blood destruction could only be demonstrated by the Coombs' [4, 5] technic of utilizing anti-human globulin rabbit serum.

CASE REPORT

A 39 year old white farmwife was admitted to the University of Virginia Hospital on May 28, 1948, complaining of nausea, vomiting, headache and weakness of three weeks' duration.

She had been in excellent health until three weeks before admission. The earliest symptoms were slight generalized weakness and lassitude. The following day she noted nausea, vomiting, headache (most prominent in the retrobulbar region), more marked weakness, chilly sensations and feverishness. Three days later her relatives noted that she had become quite pale, and one sister thought her skin and sclerae were yellow. At this time her symptoms were quite severe and she was taken to her local hospital.

It was found that her red blood cell count was 500,000 per mm.^{3} No history of acute or chronic hemorrhage could be elicited, and no evidence of bleeding phenomena was found except for scattered retinal hemorrhages. She received five transfusions of whole blood and her red count rose to 2,700,000 per mm.^{3} It was noted that she had mild febrile reactions after each transfusion. There was associated marked

* Received for publication July 21, 1949.
From the Department of Medicine of the University of Virginia Hospital.
† Now at Massachusetts General Hospital, Boston, Mass.

symptomatic improvement. However, 10 days after that admission she underwent another episode of nausea, vomiting and headache, and the red count fell once more (1,200,000 per mm.^{3}). At this time her icterus index had risen from a level of 18 to 75, the van den Bergh showed a positive indirect reaction (2 mg.), with a negative direct reaction. The reticulocyte count was high, the sternal marrow showed extreme erythroid hyperplasia, and the spleen was palpable. Tests performed in the laboratories of the University of Virginia Hospital at that time showed the following: Hypotonic saline fragility test revealed no increased fragility of the red cells; fecal urobilinogen was greatly increased, to 2,500 mg. per 100 gm. of feces; urinary urobilinogen was normal; liver function tests, including bromsulfalein retention, cephalin-cholesterol flocculation test and hippuric acid excretion were normal. Reticulocyte count was 15 per cent.

The patient was transferred to the University of Virginia Hospital on June 29. No further significant points in the history could be elicited. No associated infection, abnormal food, drug, poison intake or contact could be incriminated as a precipitating factor in the hemolytic process. Systems review, exclusive of those symptoms already mentioned, was negative except for a slight burning on urination. Menstrual history was negative, the last menstrual period having begun three days after the onset of her symptoms, with normal duration and flow. She had experienced three normal pregnancies and all three offspring were alive and well. The past medical history was completely negative except for the usual childhood diseases.

The family history, as far as could be determined, revealed no known anemias or other familial disease tendencies. Four siblings, as well as the patient's mother and husband, were alive and well. Her father had died at the age of 73 with jaundice and stomach trouble of unknown nature. The various members of the direct family were not available for hematologic studies.

The physical findings on admission included the following: Blood pressure was 96 mm. Hg systolic and 50 mm. diastolic; pulse, 96; respiration, 24, and temperature, 100° F. The patient was well developed and well nourished but pale, with a slight yellow tint to skin and sclerae. Examination of the heart showed no enlargement; there was a soft systolic murmur over the mitral and pulmonic areas. The spleen was palpable, being enlarged 2.5 cm. below the left costal margin, and was firm, smooth and nontender. The liver was not palpable.

Laboratory Studies: The initial red blood count was 1.02 mil. per mm.,^{3} with a hemoglobin of 2.7 gm. per 100 c.c. The white blood cell count was 11,000, and the differential count showed myeloid preponderance with a shift to the left. There was marked anisocytosis of the red cells, with numerous macrocytic erythrocytes and many spherocytes containing densely packed hemoglobin. Platelets were increased in number on the smear; reticulocyte count was 3.4 per cent, and there were approximately 11 nucleated red blood cells per 100 white cells. The hematocrit was 12, with an MCV of 117.6 cu. μ, MCH of 27 $\gamma\gamma$, and MCHC of 22.5 per cent. Blood cultures on five occasions were negative.

Urine examination was normal except for 1 plus albuminuria and the presence of urobilinogen to a dilution of 1/60; the blood urea was not elevated. The total urinary urobilinogen excretion was 13.12 mg. in 24 hour urine collection. Stool examination was normal except for fecal urobilinogen in a concentration of 2,400 mg. per 100 gm. of feces. Coproporphyrin was present in the urine, but uroporphyrins were not.

Bone marrow aspiration preparation on admission and on two subsequent occasions showed extreme erythroid hyperplasia of the normoblastic type. The myeloid erythroid ratio was under one on all examinations. The white cell series showed normal distribution and maturation, with no significant pathologic forms and no suggestion of a leukemic process. Multiple liver function studies yielded no evidence of

impaired function and were repeatedly normal, and no evidence of a hemorrhagic tendency was noted.

A hypotonic saline red cell fragility test showed initial hemolysis at 0.24 per cent and complete hemolysis at 0.36 per cent. Control values were 0.24 per cent and 0.36 per cent, respectively. A repeat test at a later date was also normal.

Repeated attempts to demonstrate autoagglutination were carried out. The Donath-Landsteiner reaction was negative. Incubation with and without chilling followed by centrifugation revealed no autohemolysis. Incubation at 37° C., 56° C. and 4° C. of oxalated blood and cells suspended in serum for 12 hours failed to show any agglutination or hemolysis. Adjustment of the pH to approximately 6.5 also failed to yield agglutination. Furthermore, carrying out these procedures with cells from a normal individual of the same blood type (A_1, Rh +) suspended in the patient's serum yielded negative results. The incubation of the patient's cells and homologous

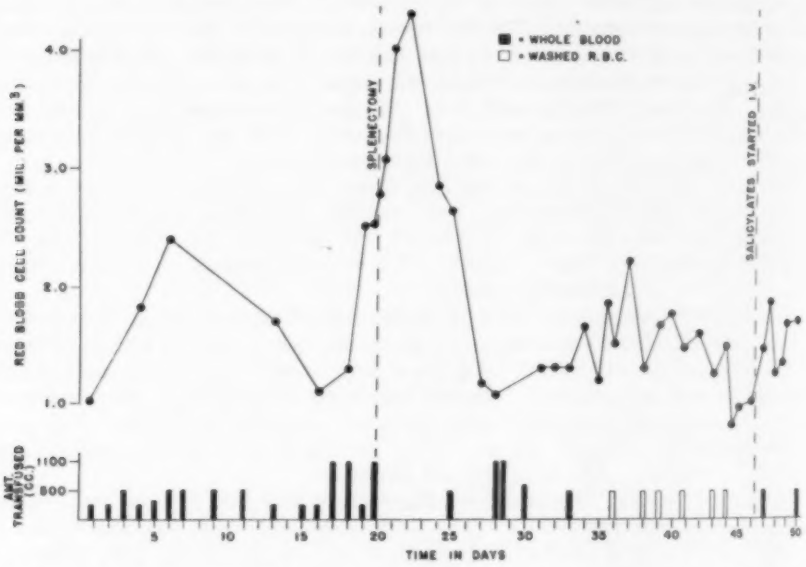


FIG. 1. The clinical course of the patient as reflected by the red count, showing response to various types of therapy.

cells suspended in normal human type AB plasma with the patient's serum in increasing dilutions also failed to demonstrate the presence of "incomplete" autoagglutinins and isoagglutinins in the patient's serum.

Clinical Course, Therapy and Special Studies: The severity of the anemia necessitated almost daily transfusion for maintenance of a circulating erythrocyte level compatible with life. There was a definite correlation of the patient's symptoms of weakness, dyspnea and apprehension with the degree of anemia, and the symptoms could be temporarily relieved by replacement therapy. During the 50 days of hospitalization she received the equivalent of 35 transfusions of 550 c.c. whole blood. It was noted that after most of the transfusions the patient had a mild febrile reaction, sometimes with an associated chill. Her daily temperature ran a low-grade relapsing course, rising from an average of 100° F. to 101° F. or 102° F. once a day, occasionally spiking to 103° F. after transfusion.

Figure 1 depicts the clinical course as reflected by the red cell count and indicates the response to various therapeutic measures. After the establishment of the diagnosis, the plan of treatment resolved itself into concerted effort to build the patient up to the point where splenectomy could be performed. Consequently, between June 14 and June 17 she received 3,500 c.c. of blood. Her red count rose from 1.1 to 2.8 mil. per mm.^{3}, the hemoglobin being 8.5 gm. per cent, hematocrit 26, and the icterus index 45 (down from a high of 75 six days previously). She was transferred to the Surgical Service on June 17.

Splenectomy was performed under ether anesthesia. No difficulty was encountered and a large spleen was easily removed. The surgeons noted no evidence of any accessory spleen in the upper abdomen. The spleen weighed 460 gm., was smooth, bluish-gray in color and rather soft. Cut section showed marked congestion and indistinct Malpighian bodies. Microscopic study showed the vessels of the pulp to be congested with red cells, some undergoing degeneration. The sinusoids were dilated and lined with cells containing large amounts of blood pigment. No extraordinary erythrophagocytosis was noted.

Within 12 hours of operation, as shown in figure 1, the red count rose to 3.1 mil. per mm.^{3} and the hemoglobin to 10 gm. per cent without any transfusions. There was marked improvement in the patient's well being, and two days after the operation she was out of bed for the first time and feeling much stronger. Wound healing was normal. After splenectomy the red count rose steadily, as shown in figure 1. Unfortunately, during this time complete blood studies were not done. The following day the red count and hemoglobin had fallen somewhat, and the patient experienced mild nausea and malaise. Icterus index was 42 and the hematocrit 15. The counts remained at about this level the next day.

On June 24, seven days postsplenectomy, she apparently experienced, subjectively, hemolytic crisis with recurrence of headache, weakness, nausea and vomiting, increasing icterus and anemia.

In spite of 1,100 c.c. of whole blood, her red count fell even lower the next day. The nucleated cell count at this time was 26,800 per mm.^{3}, about 40 per cent of which was nucleated red blood cells. Again, the patient's symptoms correlated with the severity of the anemia and the hemolytic activity. However, it was no longer possible to affect either her clinical status or blood counts by transfusion.

It was apparent that the destruction of the donated red cells was so rapid that little benefit (even, perhaps, detriment) resulted from transfusion. It was almost as though each transfusion provided more antigenic stimulation.

The patient's blood type was A_1, Rh +. The type and cross match were checked several times before each transfusion. No in vitro incompatibility was ever demonstrated. On several occasions, the donor cells for transfusion were suspended in serum rather than saline to eliminate the presence of "blocking" or "incomplete" antibodies. The anti-Rh titer of the patient's blood was negative in all dilutions for agglutination or blocking on two occasions.

Again attempts were made to detect some in vitro incompatibility by the previously described technics. Because of the remote possibility that some factor in the plasma of the donated blood may have been playing a rôle in antigenically stimulating the intense hemolytic activity, infusions of washed red blood cells, compatible in vitro and suspended in saline, were given. Although after the first few administrations of washed cells there was a rise in the red count to 2.23 mil. per mm.,^{3} it was apparent that no sustained effect resulted. Since the survival time of the transfused cells was so short, it was decided to hold off replacement therapy as long as possible and to transfuse only when the need was extreme. Within three days of the last trans-

fusion with red cells in saline, the red count was 0.81 million. On this day (July 11) the Coombs' test was first carried out.

Special Immunohematologic Studies: Anti-human globulin rabbit serum prepared by injections of human serum according to the technic of Coombs [4, 5] was utilized. One drop of a one-sixteenth dilution of the serum was added to a 2 per cent mixture of the patient's cells (type A_1, Rh +) in isotonic saline, the cells having been washed, centrifuged and re-suspended six times. Using the slide technic, the patient's cells were strongly agglutinated at room temperature in one minute. Control normal type A_1, Rh + washed cells were not agglutinated in one hour.

Following this initial demonstration of autoagglutinins, corollary procedures to detect isoagglutinins were carried out. Washed normal type A_1, Rh + red cells were suspended in the patient's serum and incubated 15 minutes at 37° C. No agglutination occurred. These cells, with the antibody presumably adsorbed to their surfaces, were washed six times in isotonic saline and resuspended in a 2 per cent concentration in saline. These "sensitized" cells were set up for the Coombs' test as previously described. Agglutination was noted in one minute, demonstrating the isoagglutinins which were participating in the destruction of normal transfused homologous red cells.

It was logical to theorize on the possibility of finding some substance which might inhibit the antigen-antibody reaction, which in this case was represented by red cell combination with blocking or incomplete antibodies. Because of the patient's downward course, it was realized that extensive screening of many compounds by well controlled technics was not possible at the time. Neither pyribenzamine or heparin had any inhibitory effect on the sensitization of normal cells. In fact, heparin seemed to enhance the degree and speed of agglutination. Salicylates were tested because of previous tentative evidence that they bring about attenuation of the antigen-antibody reaction and the resultant histologic changes in rheumatic fever.[7, 8] Furthermore, Homburger [9] has demonstrated inhibition of Rh antibody production in immunized animals by sodium salicylate. Acetyl salicylic acid in large amounts completely inhibited the adsorption of incomplete antibody from the patient's serum by normal A_1, Rh + cells when added to the incubating mixture of normal cells and the patient's serum. Concentrations of sodium salicylate or acetyl salicylic acid within the range of maximal therapeutic blood levels, i.e., 40 to 45 mg. per 100 c.c., seemed to retard the sensitization of normal cells, but did not completely inhibit the process.

With the realization that the condition of the patient was rapidly deteriorating, it was decided that a trial of massive salicylate therapy was justified even though the experimental evidence for its efficacy was far from complete. A transfusion was given simultaneously with the slow infusion of 6 gm. sodium salicylate in 500 c.c. of 5 per cent glucose in water, and symptoms of severe toxicity ensued, with tinnitus, dimness of vision and nausea and vomiting. Blood drawn from the patient at the height of toxic symptoms was tested for its blocking antibody activity. Unfortunately, a plasma salicylate level was not performed at this time. Washed normal red cells were suspended in: (1) Normal serum as a negative control; (2) the patient's serum collected before salicylate therapy as a positive control; (3) the patient's serum collected at the height of salicylism.

Each was incubated 15 minutes at 37° C. The cells in each tube were removed by centrifugation, washed six times with normal saline and resuspended as a 2 per cent concentration of cells in saline. One drop of each cell suspension was then mixed with one drop of one-sixteenth dilution of rabbit anti-human globulin serum. The negative control showed no agglutination in five minutes. The positive control showed strong agglutination in 30 seconds. The cells which had been suspended in the patient's serum collected at the peak of toxic symptoms of salicylism, presumably

when the concentration of salicylates was very high, showed no agglutination in two minutes. There was slight microscopic agglutination in five minutes.

This initial demonstration of partial inhibition of the sensitization of normal red cells by the circulating blocking antibody was the only time that in vitro evidence of a beneficial effect of the administered salicylate could be detected. Repeated attempts to duplicate the above results were futile. Nevertheless, salicylate treatment was continued, but because of the patient's extreme nausea and vomiting the dosage was necessarily limited. A plasma level of salicylates above 30 mg. per 100 c.c. could never be attained. This fact might explain the inability to show any effect of salicylates subsequent to the initial demonstration of a diminution of activity of the antibody in the patient's serum drawn at a time when the symptoms of salicylism were alarming.

Concomitant with a brief slight rise in the red count following institution of salicylate therapy (from 1.02 mil. to 1.88 mil. in one day), the patient felt considerably better. However, the next day the clinical status was again poor. She died rather suddenly three days later, on July 17, 1948. At the time of death, there were numerous petechial lesions over her face and trunk. The blood was dark reddish-green in color and failed to clot readily.

Unfortunately, permission for postmortem examination was not obtained.

Discussion

The severity of the hemolytic process in this case was so intense that the transfused homologous red cells, even though compatible in every case by the standard methods of cross matching, were destroyed almost immediately. This fact alone bespoke the presence of a substance or substances in the circulating blood which so altered the normal transfused cells that hemolytic destruction occurred rapidly. It seems pertinent that these abnormal antibodies, which no doubt were present in high titer, could be detected only by the Coombs' technic. This emphasizes the importance of utilizing all the available methods for the demonstration of hemolytic or agglutinating antibodies in cases of idiopathic hemolytic anemia.

The results of splenectomy were quite interesting. It was our hope that the rapid defervescence of the process following this procedure would be permanent. The recurrence and continuation of the hemolytic activity beginning seven days postsplenectomy indicated that only temporary cessation had resulted. The exact rôle of the spleen in the red cell destruction in hemolytic anemias is not fully known. However, a dual action, in which it serves both as a repository for the stasis and mechanical disintegration of sensitized red cells and as a partial source of antibody formation, as advanced by Dameshek,[10] would seem probable. One can speculate that, in this case, removal of the spleen ablated a major site of red cell destruction and also a segment of the reticuloendothelial system responsible for antibody formation. However, this beneficial effect was soon overcome by intensification of the morbid process elsewhere in the body. It appears probable that the continued production of abnormal antibodies was important in the rapidly progressive hemolytic activity.

Although the initial in vitro evidence and the immediate clinical results were encouraging, it was soon apparent that salicylates were not significantly slowing the hemolytic activity. Nevertheless, the observation that salicylates, albeit in

relatively great concentrations, could diminish the sensitization of normal cells by this patient's blood is of interest, and suggests an approach which may be of benefit in other cases of this type.

Summary

1. A case of acute idiopathic hemolytic anemia of severe degree is presented.

2. Autoagglutinins and isoagglutinins in the patient's serum could be detected by the Coombs test, but by no other means.

3. The clinical course is presented, showing marked temporary improvement following splenectomy but later resumption of the hemolytic process.

4. The in vitro inhibition of the action of isoagglutinins by salicylates prompted the therapeutic trial of massive salicylate administration. Although some evidence was obtained that this treatment slowed the hemolytic activity, the general course of the disease was not altered and the patient died.

5. The importance of utilization of all present technics for agglutinin or hemolysin demonstration in such cases is stressed. The theoretic effect of splenectomy and the possible significance of salicylate therapy in this case are discussed briefly.

Acknowledgment

The author wishes to acknowledge with appreciation the assistance and advice of Dr. Byrd S. Leavell and Dr. O. B. Bobbitt, of the University Hospital, in the study of this case.

BIBLIOGRAPHY

1. Dameshek, W., and Schwartz, S. O.: Acute hemolytic anemia (acquired hemolytic icterus, acute type), Medicine **19**: 231–327, 1940.
2. Wiener, A. S.: A new test (blocking test) for Rh sensitization, Proc. Soc. Exper. Biol. and Med. **56**: 173–176, 1944.
3. Race, R. R.: "Incomplete" antibody in human serum, Nature, London **108**: 771–772, 1944.
4. Coombs, R. R. A., Mourant, A. E., and Race, R. R.: In vivo isosensitization of red cells in babies with hemolytic disease, Lancet **1**: 264–266, 1946.
5. Boorman, K. E., Dodd, B. E., and Loutit, T. F.: Hemolytic icterus, congenital and acquired, Lancet **1**: 812–814, 1946.
6. Dameshek, W., and Bloom, M. L.: The events in the hemolytic crisis of hereditary spherocytosis with particular reference to the reticulocytopenia, pancytopenia and an abnormal splenic mechanism, Blood **3**: 1381–1410, 1948.
7. Coburn, A. F., and Kapp, E. M.: Effect of salicylates on precipitation of antigen with antibody, J. Exper. Med. **77**: 173–183, 1943.
8. Coburn, A. F.: Salicylate therapy in rheumatic fever: rational technic, Bull. Johns Hopkins Hosp. **73**: 435–464, 1943.
9. Homburger, F.: Sodium salicylate inhibition of anti-Rh immunization in animals, Proc. Soc. Exper. Biol. and Med. **61**: 101–102, 1946.
10. Dameshek, W.: Hemolytic mechanisms, Ann. New York Acad. Sc. **48**: 685–703, 1947.

SEVERE SPONTANEOUS HYPERSENSITIVITY TO HEPARIN *

By ALEXANDER GOTZ, M.D., *Ann Arbor, Michigan*

IN recent years, heparin has found wide clinical use as an effective agent in the prevention and treatment of thromboembolic disease.

Heparin is a complex organic substance containing chondroitinsulfuric acid and small amounts of protein (1 to 2 per cent).[1] It is usually obtained from beef liver or lung. It would therefore seem quite likely that a fairly large number of cases of sensitivity to this substance would be encountered in clinical practice. Surprisingly, however, the literature contains comparatively few reports of heparin sensitivity.

Jorpes [2] mentioned four cases in his comprehensive monograph, without going into detail about them. Hojensgard and Schwartz,[3] in a recent review, mention four cases from Sweden, all of which occurred before 1942 and may have been due to impurities present in the product available at that time. All four patients developed their symptoms either some time after therapy with heparin had been in progress, or after renewal of such therapy after an interval without it. The same authors include the report of a recent case of their own, where a patient was given 150 mg. of heparin intravenously for the first time in his life. Immediately following the injection the patient developed marked flushing of the skin and complained of distress. This disappeared a few minutes later and was followed by generalized urticaria, which lasted several hours. There was no edema, and no respiratory distress. Intracutaneous tests with heparin from the same ampule, from a different ampule of the same manufacturer, and from that of a different manufacturer were all strongly positive. Passive transfer tests done with blood drawn three hours after the attack were negative. The patient was not tested for beef allergy. Grolnick and Loewe [4] reported a case of subacute bacterial endocarditis treated with penicillin and heparin. The patient developed erythema and hives. Skin tests and passive transfer tests were positive only with heparin. Later, positive passive transfer reactions were also obtained with beef serum and beef lung.

Levy and McKrill [5] observed reactions occurring daily in patients receiving penicillin by intravenous drip with the addition of heparin. The reactions were characterized by fever, sometimes up to 108° F., chills, mild excitement and some disorientation. Crockett and Rhoads [6] reported a similar hyperthermic reaction in a patient receiving penicillin with heparin for subacute bacterial endocarditis. This patient had received penicillin alone for 14 days without untoward effects. When heparin, in the amount of 20 mg. per 1,000 c.c. intravenous solution, was added in order to prevent plugging of the needle, the temperature rose from normal to 105.2° F. The patient's condition worsened rapidly and he was moribund when this medication was stopped. Within a few hours the temperature dropped to normal and remained so thereafter. Several weeks later an intravenous infusion of penicillin and heparin was given to the same patient without untoward results. At this time a different lot number of heparin was used. A very interesting statement was made by DeTakats,[7] who reported that a surprising number

* Received for publication April 21, 1950.
From the Medical Service, St. Joseph's Mercy Hospital, Ann Arbor, Michigan.

of individuals have an increased reactivity to heparin, even though they had never received heparin before. This may be accompanied by flushing of the face, bronchospasm, edema or urticaria. Unfortunately, his paper does not contain details with respect to his patients.

The severity of the immediate reaction to heparin in the case reported herein, and its possible relation to the unfavorable course which the patient's illness took, seem to be of sufficient interest to warrant its presentation.

Case Report

A 59 year old male executive was admitted to the hospital three days following the onset of retrosternal pain which radiated into both arms. Electrocardiogram was diagnostic of a recent anterolateral myocardial infarction. The patient was an asthmatic individual, but was free of asthma at the time of admission. It was decided to start anticoagulant therapy, and an intravenous infusion containing 300 mg. of heparin sodium in 1,000 c.c. of 5 per cent glucose in distilled water was begun at 6:30 p.m. The rate was regulated at 20 drops per minute. The tubing used was of the disposable plastic type furnished with each individual flask of solution. At 7:00 p.m. the patient, who had been quite comfortable and had experienced no respiratory distress, became suddenly extremely dyspneic and deeply cyanotic. His respirations assumed the loud wheezing quality of bronchial asthma, and within a few minutes he was covered with giant urticaria. He required intravenous administration of aminophyllin and an oxygen tent to overcome the attack, which threatened his life. Subsequent electrocardiograms did not show an extension of the infarct, but he slipped into a state of profound myocardial insufficiency and succumbed four and one-half months later.

Discussion

This patient had never received heparin before. At the rate of infusion of 20 drops per minute he had not received more than 10 mg. of heparin at the time his asthmatic attack exploded. No other medication had been given at the time, nor did his room contain flowers or any objects to which he was sensitized. This patient had undergone repeated and extensive allergy studies at the University of Michigan Hospital. He had never shown sensitivity to beef, pork or any other meat. Thus it becomes quite probable that this patient's severe sensitivity reaction was due to heparin. It remains speculative whether heparin itself or some concomitant impurity produced the reaction.

Cortes, Grolnick and Loewe [8] reported that guinea pigs sensitized with heparin and studied by the Schultz-Dale technic did not show any evidence of sensitization. Gregoire [9] was able to demonstrate that heparin had protective qualities when injected into sensitized rabbits shortly before reinjection of the antigen. It attenuated or suppressed the Arthus phenomenon in these animals.

Jorpes [10] also stated that heparin had protecting effects on sensitized pigeons and guinea pigs. Animal experiments by Reed-Lamson and Reynert-Winterstein, as cited by Hojensgard and Schwartz,[8] confirmed the impression that pure heparin is lacking in antigen power.

All the above quoted evidence would be in favor of those who think that sensitivity reactions obtained with heparin are due to impurities still present in the product available at this time.

On the other hand, Giordano [11] used a combination of heparin, acetyl choline

and histamine in desensitizing allergic patients. This was based on the assumption that all these were contained in the substance "H." The prolonged clotting time found in anaphylactic shock may be due to a release of heparin or a heparin-like compound.

As far as the clinical use of heparin is concerned, it was pointed out by Jorpes that small "test doses" of 25 mg. of heparin might be used in patients suspected of being easily sensitized. The present case would tend to prove that even that dose might be found to be dangerously high in a very sensitive individual, and that it might be safer to use the intracutaneous technic than the intravenous one.

Summary

1. The recent literature pertaining to heparin sensitivity is reviewed.

2. It is pointed out that by far the majority of reported cases of heparin sensitivity are due to gradual sensitization to this substance.

3. A case is presented of a patient who had never received heparin before and who experienced a severe attack of bronchial asthma associated with giant urticaria after a dose of heparin not exceeding 10 mg.

4. The cause of the reactions as being due either to heparin itself or to concomitant impurities is discussed.

5. It is suggested that great care should be employed in the administration of heparin to allergic individuals, and that test doses smaller than 10 mg. should be used intracutaneously.

Addendum

Since the completion of the present case report, a very similar case of anaphylactic reaction to heparin was presented by Amoz I. Chernoff (New England J. Med. 242 : 315, 1950). The patient, a 54 year old male, was admitted to the hospital with an acute myocardial infarction and was given heparin intravenously. About one minute after completion of the injection he became deeply cyanotic and went into shock, with asthmatic breathing and a generalized macular rash. The total dose of heparin given in this case was 50 mg., about five times the amount given to our patient. In Chernoff's case there was no history of asthma or other allergy.

Immunologic studies were carried out on this patient and were positive to pork and beef, and less strongly to various preparations of heparin. The author concluded that this case may represent a true hypersensitivity to heparin.

Acknowledgment

The author wishes to express his gratitude to Dr. John M. Sheldon, Chief of the Allergy Clinic, University of Michigan Hospital, for permission to use information from his records, as well as for his kind interest and valuable advice.

BIBLIOGRAPHY

1. Jorpes, E.: Personal communication.
2. Jorpes, E.: Heparin in the treatment of thrombosis, 2nd Ed., 1946, Oxford, New York, p. 165.

3. Hojensgard, I. C., and Schwartz, M.: Heparin hypersensitivity, Acta Allergologica 2: 7, 1949.
4. Grolnick, M., and Loewe, L.: Report of sensitivity to heparin in patient, J. Allergy 18: 277, 1947.
5. Levy, L., II, and McKrill, N.: Results in the treatment of subacute bacterial endocarditis, Arch. Int. Med. 77: 367, 1946.
6. Crockett, K. A., and Rhoads, P. S.: Hyperthermia caused by penicillin-heparin in the treatment of subacute bacterial endocarditis, Ann. Int. Med. 28: 456, 1948.
7. DeTakats, G.: Thrombo-embolism, J. internat. chir. 8: 903, 1948.
8. Cortes, J. L., Grolnick, M., and Loewe, L.: Anaphylactogenic properties of heparin in guinea pigs, J. Allergy 18: 196, 1947.
9. Gregoire, C.: Influence de l'heparine sur les réactions d'anaphylactie cutanée, Arch. internat. de pharmacodyn. et de thérap. 72: 76, 1946.
10. Jorpes, E.: See reference 2, p. 55.
11. Giordano, A. F.: Association of histamine with acetylcholine and heparin in the treatment of allergies, Día méd. 19: 848, 1947.

SERUM NEURITIS *

By Isidore Fischer, M.D., *New York, N. Y.*

Serum sickness has been estimated to follow the injection of various sera in about 15 per cent of all cases in which they are used.[1] There is no known method of preventing it, nor is there any way of identifying the persons likely to develop it. The whole subject, in fact, remains in need of clarification. It was originally attributed to the presence of antibodies in the serum, but that assumption, as Doyle [2] notes, was promptly disposed of when Johannessen demonstrated that the reaction also occurred following the injection of horse serum alone. Although the exact cause is still to be established, a number of factors have been shown to be at least partially responsible, including the size of the dosage, the age of the serum, the degree of purification and concentration, the type of organisms employed, the route of administration, and the animal from which the serum is obtained. The individual reaction to the injection is another factor of considerable importance.

Serum sickness may develop any time between the sixth and fourteenth days after the serum injection but is most frequent between the sixth and eighth or ninth days. The chief manifestations are local itching and swelling, generalized urticaria, fever, lymphadenopathy, polyarthritis, malaise, leukopenia, albuminuria, fall of blood pressure and decreased coagulability of the blood. Not all of these manifestations are likely to be present in the same case. As a rule, serum sickness is a transient affection, which responds promptly to the proper treatment (chiefly adrenalin) and which terminates in complete recovery. Occasionally, however, it is followed by the so-called serum neuritis, of which the following case is an example. So far as can be determined, this is the first case to be reported in which there was a marked psychotic factor.

* Received for publication May 6, 1950.
From the Bronx Hospital, New York.

Case Report

A 41 year old married white woman sustained a laceration of the left elbow and right middle finger September 15, 1948, as the result of a fall. The laceration was sutured and a prophylactic injection of 1,500 units of tetanus antitoxin was given intramuscularly in the upper anterior portion of the right arm immediately after the accident. The wound healed without complications.

Eight days after the accident the patient began to complain of itching and urticaria and within a short time presented the typical picture of serum sickness. At the same time she complained of moderate pain in the left shoulder. She promptly responded to treatment with adrenalin and pyribenzamine. Forty-eight hours later she began to complain of continuous, extremely severe pain, which was greatly increased by movement, in the right shoulder, radiating to the right scapula and down the right arm. A few hours after the onset the right forearm and hand became very much swollen. The patient was treated at home until October 7 (that is, until the twenty-third day after the accident), when she was admitted to the medical division of the Bronx Hospital (service of Dr. Max Weiss) because heavy sedation combined with several hypodermic injections of demerol (50 mg. each) had failed to control the pain.

Inquiry into the previous history revealed nothing suggestive of an allergic tendency and also revealed no other fact of interest beyond a story of social difficulties on a poor family background. The patient, who had been brought up in an orphanage, admitted to an intense dislike for her mother and was said to cry at the slightest provocation and to suffer fainting spells when she became angry or excited.

Physical examination revealed a well developed and well nourished white woman who was evidently in a highly emotional state. She complained bitterly of continuous, severe pain in the right shoulder, seemed over-anxious about her condition, and several times burst into tears in the course of the history-taking and examination.

The general examination was entirely negative, all evidence of the serum sickness having disappeared. The blood pressure was 110/70 mm. Hg. The corneal and gag reflexes were not elicited but other reflexes were hyperactive. The neck was flaccid but the patient complained of pain when it was flexed. The right upper extremity was held in flexion, the power of abduction apparently being lost. There was marked tenderness on pressure over all the shoulder muscles and deltoid region and moderate tenderness over the area supplied by the fifth and sixth cervical nerves. No gross atrophy of the regional structures was apparent, and passive motion of the right shoulder and right arm was possible. The strength of the hand-grip on the right was considerably less than on the left. There were no other evidences of motor impairment or sensory disturbances.

All laboratory examinations, including blood serologic tests, were negative. Roentgenologic examination of the right shoulder, elbow and hand revealed no abnormalities. The pain of which the patient had complained on flexion of the neck was explained by the roentgenologic demonstration of marked hypertrophic changes and lateral bridging from the second to the fourth cervical vertebrae.

A neurologic consultant reported definite weakness of the muscles innervated by the musculocutaneous and radial nerves. Electromyograms revealed paralysis of the right axillary nerve.

The patient remained in the hospital for 14 days. The brachial neuritis showed some improvement under immobilization, general supportive and vitamin therapy, and the local application of heat. Her mental and emotional status, however, deteriorated. She continued in a highly emotional state, with frequent outbursts of crying, complaints of insoluble personal problems, and summing up of the past and its unhappy contribution to her life. At the end of this time, on the advice of a con-

sultant psychiatrist, she was removed to another institution, where she remained for the next eight months. She was reëxamined in July, 1949, 10 months after the onset of the serum neuritis. At this time abduction of the right arm was possible, but there was marked atrophy of the muscles of the right shoulder and upper arm and there was considerable difference in the strength of the hand-grip on the right and left sides. The muscles of the neck were stiff, and weaker than on the first examination. There had been a moderate weight loss. The patient seemed somewhat more stable emotionally as the result of the intensive psychiatric therapy she had received during the eight-month period of hospitalization.

Discussion

The first reported neurologic complications of serum sickness, according to Bennett,[3] were observed by Gardère and Gangolphe in 1908. Similar observations were made by Vincent and Richet (fils) [4] in 1911. Whether serum neuritis was more frequent in France than elsewhere, or merely attracted more attention there, is not clear, but, whatever the reason, the majority of cases have been reported from that country. According to Bennett,[3] some 70 had appeared in the French literature up to 1938. The first American case was recorded by Richardson [5] in 1917, and the first English case, in a battle casualty, by Dyke [6] in 1918. Mishkin,[1] writing in 1949, stated that up to that time approximately 100 cases of the Erb-Duchenne type of involvement had been reported, the majority being on the right side.

The most complete reviews of the literature of serum neuritis were made by Doyle [2] in 1933 and by Bennett [3] in 1939. Doyle, in 1933, was able to find only 47 cases which he regarded as completely authentic. In 34 of these the neuritic involvement had followed the injection of tetanus antitoxin. The majority of patients were males, as might be expected, because males are more prone to accidents. The remaining cases followed injections of diphtheria antitoxin (seven), scarlet fever antitoxin (five), antipneumococcic serum (two) and antimeningococcic serum (one). The brachial plexus was affected in 34 cases; all the patients exhibited motor disability and about a quarter exhibited sensory changes. Fibers from the fifth and sixth cervical nerves, that is, the cephalic portion of the brachial plexus, were most often affected, though not all of the fibers of an affected muscle were necessarily involved.

Involvement of the cerebral, meningeal and spinal cord nerves has been reported following serum sickness, and optic involvement, polyneuritis and poliomyelitic forms have also been reported. Involvement of the peripheral nerves is, however, by far the most frequent manifestation, though why they should be selectively affected is not clear. Bourgignon (cited by Doyle [2]) advanced the hypothesis that tetanus antitoxin selects nerves with low chronaxie, while diphtheria antitoxin selects those with medium chronaxie; but, as Doyle [2] points out, a mere analysis of reported cases is sufficient to show that this reasoning does not hold. Another hypothesis is that serum neuritis is primarily vascular in origin, vasodilatation, perivascular infiltration and hemorrhage producing nerve-cell and fiber death. Foster Kennedy,[7] who reported six cases of neurologic involvement following serum sickness, offered toxicity of the serum or urticarial edema of the perineural tissues as possible causes.

Neuritic symptoms as a rule occur when serum sickness is most intense, although they may appear almost immediately after the onset or when the attack

has almost disappeared. The course of events is usually severe pain in the neck, shoulders, arms or legs, followed, within hours or days, by flaccid paralysis, muscle tenderness and muscle atrophy. Loss of weight is frequently marked. The pain may disappear promptly or may last for days, weeks or even months. It is characteristically extremely severe. All of the reported cases indicate that analgesics and narcotics supply little or no relief, and many authors speak of the patients as "walking the floor" in their agony.

While some 20 per cent of all patients, according to Thompson and Tombleson,[5] are left with permanent residua in the form of impaired motion and loss of strength in the affected extremity, the majority of victims of serum neuritis respond with a reasonable degree of promptness to such measures as immobilization of the affected part, general nutritive and vitamin therapy, local application of heat and, later, physiotherapy with graduated exercise. Artificial fever therapy has been helpful in some cases. In one of Bennett's [3] personal cases the patient, who had had no treatment for the first five months of his illness, was completely relieved of severe pain after six artificial fever treatments, but at the end of a year he showed no functional improvement at all. In this case, as Doyle [2] pointed out in the discussion of Bennett's report, profound atrophy of the muscles must have occurred over the period when the patient was receiving no treatment.

In the discussion which followed Bennett's presentation, it was brought out by Brahdy that recurrence of serum neuritis is a definite possibility if additional antitoxin should be necessary in the future. His patient recovered completely within a few months but had a recurrence three years later, when a second injection of tetanus antitoxin had to be given. This time the paralysis was still present at the end of three years. The patient had an alcoholic background, though whether that fact played any part in the chain of events is not brought out.

Serum neuritis is extremely uncommon. Although hundreds of prophylactic injections of tetanus antitoxin are given in the Bronx Hospital every year, the case reported in this communication is the only instance of the condition found in an exhaustive review of the record library files. Bennett's [3] experience, which included five personally observed cases, is most unusual. His warning, therefore, of the possible medicolegal aspects of this complication, particularly in industry, deserves careful consideration. While warning—as do other observers—that the possible risk of serum sickness and serum neuritis is in no way comparable to the possible risk of omitting prophylactic tetanus antitoxin, Bennett points out that the condition is compensable if it follows an industrial injury. For this reason he suggests that physicians exercise discretion in their administration of tetanus antitoxin and limit its use to cases in which it is clearly indicated. In other words, while it should always be used in patients with dirty or penetrating wounds, it should not be given for trivial reasons, or even routinely.

Bennett's attempt to secure the experience of leading insurance companies with serum neuritis was not particularly successful. Six of 11 companies which replied to his inquiry had had no claims from this cause. Three acknowledged claims but gave no details. One of the two remaining companies reported a case of right brachial neuritis with aphasia which developed at the height of serum sickness. The disability lasted for six months and compensation amounted to more than $2,000. The other company reported two cases. One patient, whose

disability lasted for five months, received a total of $500. The second patient, at the time of the inquiry, was still being carried on a basis of 50 per cent disability, but the total amount of the compensation he had received was not stated. Possibly this is the patient in Bennett's own series who had no treatment for five months; it is stated that eight months after the original injury he was still receiving compensation on the basis of a 50 per cent permanent disability.

These various facts clearly indicate the importance, from the medicolegal standpoint, of warning patients who have received tetanus antitoxin and who are not hospitalized to report promptly the development of any untoward symptoms, so that energetic treatment may be instituted at once.

In most respects, the case reported in this communication fits into the pattern of other recorded cases. Serum sickness developed on the eighth day after a prophylactic injection of tetanus antitoxin and was, as usual, transient. Serum neuritis developed 48 hours later. All manifestations had completely disappeared when the patient was hospitalized except for the local neuritic complication. There was, as usual, nothing in the previous history to suggest that serum sickness might develop. The serum neuritis affected the brachial plexus, as it most often does, and the history of the intractability of the pain, in spite of ample sedation and analgesic medication, is entirely typical. The diagnosis, in fact, could have been made on the history and this phenomenon alone. The single unusual feature in the case is the strongly psychotic background. It probably had nothing to do with the development of the serum neuritis, but the serum sickness and subsequent neuritis undoubtedly precipitated the psychotic episode for which a long period of treatment was necessary. Under the circumstances, functional recovery was as good as could have been expected.

Summary

1. A case of serum sickness is reported in which serum neuritis followed in a patient with a strongly psychotic background.

2. Certain important features of serum neuritis, as they are emphasized in the literature, are reviewed. Particular attention is called to the possible medicolegal aspects of the condition.

BIBLIOGRAPHY

1. Mishkin, J. A.: Unusual reactions to tetanus antitoxin, New York State J. Med. 49: 292–293, 1949.
2. Doyle, J. B.: Neurologic complications of serum sickness, Am. J. M. Sc. 185: 484–492, 1933.
3. Bennett, A. E.: Horse serum neuritis. With a report of five cases, J. A. M. A. 112: 590–596, 1939.
4. Vincent, C., and Richet, Ch. (fils): Forme atypique de la maladie du sérum; accidents tardifs et graves, Bull. et mém. Soc. méd. d. hôp. de Paris 32: 670–681, 1911.
5. Richardson, W. W.: Tetanus, with secondary multiple neuritis. Report of a case with recovery, J. A. M. A. 68: 1611–1612, 1917.
6. Dyke, S. C.: Peripheral nerve lesions after antitetanic serum, Lancet 1: 570, 1918.
7. Kennedy, F.: Certain nervous complications following the use of therapeutic and prophylactic sera, Am. J. M. Sc. 177: 555–559, 1929.
8. Thompson, A. R., and Tombleson, J. B. L.: Some neurological complications of serum therapy, Brit. M. J. 1: 1015–1016, 1940.

A CASE OF HAND-SCHÜLLER-CHRISTIAN SYNDROME TREATED WITH CORTISONE *

By WILLIAM H. BLAHD, M.D., *Los Angeles,* MARVIN S. LEVY, M.D., *Beverly Hills,* and SAMUEL H. BASSETT, M.D., *Los Angeles, California*

IN 1893, under the title "General Tuberculosis," Hand [1] reported a case of a three year old child with a peculiar skin eruption, skull defects and yellow nodules in the liver and spleen. Kay [2] in 1905 described diabetes insipidus, skull defects and exophthalmos in a seven year old child, which he termed "acquired hydrocephalus with atrophic bone changes." Some years later Schüller [3] and Christian [4] described cases exhibiting essentially the same clinical manifestations, and attributed these changes to pituitary dysfunction. This original concept was altered, however, by the histologic studies of Rowland [5] in 1928, which indicated that the syndrome was related to the xanthomatous diseases. Rowland postulated an inherent disturbance in lipoid metabolism, with abnormal lipoid storage in the reticuloendothelial system resulting in reactive hyperplasia and granuloma formation. Rowland's concept dominated medical thought for a decade or more, until Thannhauser and Magendantz [6] demonstrated that normal concentration of cholesterols and lipoids were found in the serum of cases presenting the syndrome described by Hand, Schüller and Christian, in contrast to other xanthomatous diseases. They contended that the disease syndrome did not represent a primary disorder of lipoid metabolism, but rather a constitutional disorder of intracellular cholesterol metabolism, ultimately leading to the formation of "foam cells" and xanthomata. Thannhauser and Magendantz termed this condition "essential xanthomatosis of the normocholesteremic type." In recent years, as a result of the investigations of Holm, Teilum and Christensen,[7] Jaffe and Lichtenstein [8] and Farber,[9] a definite pathologic relationship has been established between Hand-Schüller-Christian's syndrome, eosinophilic granuloma of bone, and Letterer-Siwe's disease (acute reticuloendotheliosis), an acute fulminant disease of children. Hand-Schüller-Christian's syndrome, then, according to present concepts, appears to be one manifestation of a systemic disease involving the reticuloendothelial system, which may manifest itself as an isolated, self-limiting lesion (eosinophilic granuloma of bone), a chronic, slowly progressive condition (Hand-Schüller-Christian syndrome), or a rapidly fatal generalized disease with multiple organ involvement (Letterer-Siwe's disease). Thannhauser [10] proposed the name "eosinophilic xanthomatous granuloma" to embrace all phases of the disease process.

The fundamental etiology of this condition is not known, although the pathologic physiology is reasonably well established. An infectious etiology has been postulated, but no specific pathogenic organism has been isolated. Thannhauser

* Received for publication March 12, 1951.

From the Medical Service, Wadsworth Hospital, Veterans Administration Center, Los Angeles 25, California.

Reviewed by the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions of the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

has suggested a blastomatous etiology because of the granulomatous nature of the lesions. The possibility of an allergic etiology has been considered and is supported by the characteristic eosinophilic histiocytoma, typical of early lesions and the frequently observed eosinophilia.[10]

Case Report

A 29 year old white male industrial engineer, of Swedish, English and Irish ancestry, was admitted to the medical service of the General Hospital, Veterans Administration Center, Los Angeles, California, on December 12, 1949, for the second time. He complained of headaches, chest pain, backache and cough of increasing severity of three to four weeks' duration.

The patient was in good health when he entered the military service in 1940. He contracted gonorrhea in 1942 and was treated for a period of 89 days, during which time an allergy to sulfonamides was noted. In 1943 he developed a perforation of the left tympanic membrane thought to be a consequence of aviation cadet training. He received a certificate of disability discharge the same year because of persistent middle ear drainage. The ear continued to drain for many months, finally subsiding in 1946.

In the spring of 1947, discharge from the left middle ear recurred but this time was associated with bilateral axillary lymphadenopathy. Both of these conditions subsided spontaneously within three months.

In the spring of 1948, he developed a persistent dry, hacking cough. Several months later he again noticed bilateral axillary swellings. These were painful and the patient was unable to adduct his arms completely. The swellings gradually disappeared over a period of two months and there has been no similar recurrence. At this time he also noticed lack of energy and gradual weight loss. In March, 1948, he noted increasing thirst and marked polyuria. In June, 1948, a roentgenogram of the chest was taken by a mobile roentgen-ray unit. He was subsequently advised to consult his private physician. The diagnosis of sarcoidosis with diabetes insipidus was made. Since the urine volume had progressively increased to four quarts daily, the patient was given "pituitary shots" by his doctor. In December, 1948, he found it necessary to stop working because of increasing weakness, productive cough, shortness of breath and intermittent ankle edema. In January, 1949, he was admitted to the Wadsworth General Medical and Surgical Hospital of the Veterans Administration Center, Los Angeles, California, for the first time. He was urinating approximately 12 quarts in 24 hours. Physical examination was not remarkable except for prominence of the eyes and the presence of several discrete brownish skin lesions on the back. These lesions were later biopsied and were negative for sarcoidosis. Numerous laboratory studies, including a glucose tolerance test and determinations of serum calcium, phosphorus, iodine, cholesterol and total proteins, were all within normal range. Sputums were negative for acid-fast organisms. Skin tests for coccidioidomycosis, histoplasmosis and tuberculosis were also negative. A roentgenogram of the chest (figure 1) showed dense interstitial fibrotic changes in both upper and middle lung fields which were interpreted as consistent with the diagnosis of sarcoidosis. Roentgenograms of the hands and skull were negative. During hospitalization the patient's excessive urine volume was controlled with difficulty by daily injections of pitressin tannate in oil. In view of the persistent suggestive pulmonary findings, the diagnosis of sarcoidosis with diabetes insipidus was retained until the patient was discharged in April, 1949.

In May, 1949, he suddenly developed a left spontaneous pneumothorax and was hospitalized at Long Beach Naval Hospital. Several thoracenteses were done and bloody fluid was removed from the chest. During hospitalization a biopsy of the

left biceps muscle was taken and was reported to be negative. While in the hospital he was instructed to use pituitary snuff. He continued this medication after leaving the hospital but, because of severe irritation of the nose and throat, he was forced to discontinue its use approximately one month before the current hospital admission. His urinary output increased markedly, and his sleep was interrupted by severe nocturia. Coughing and chest pain likewise increased in severity during the month preceding admission.

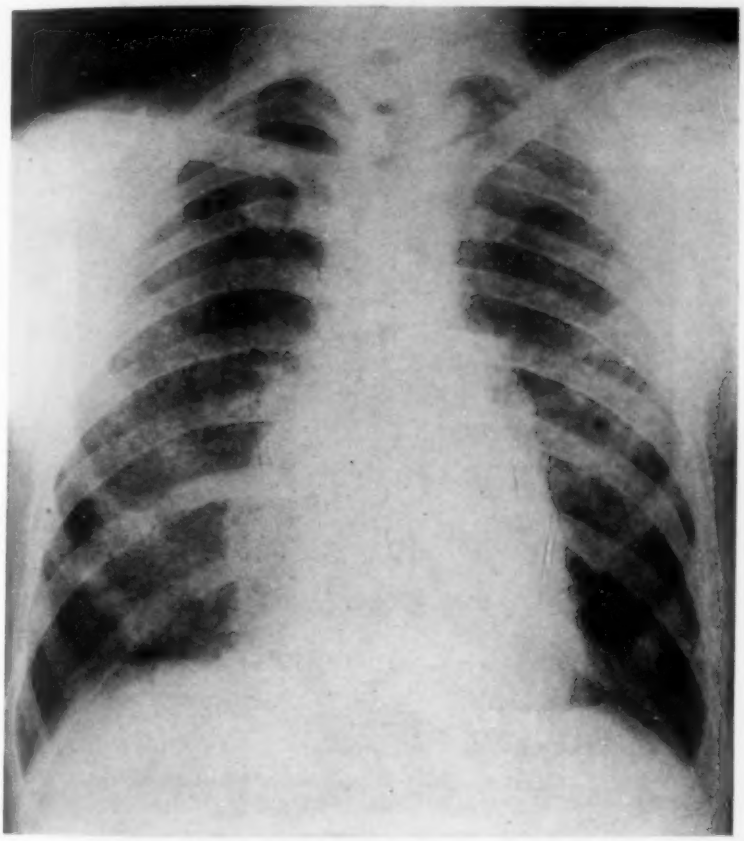


FIG. 1. Dense interstitial fibrotic changes in both upper and middle lung fields.

Family history was essentially noncontributory. The patient's father had died of uremia at the age of 56. His mother and two siblings were living and in good health. There was no history of familial or hereditary disease.

Physical examination at the time of the present admission revealed a well-developed, thin white male who appeared chronically ill. There was considerable prominence of the eyes and noticeable lid-lag. The pupils were normal bilaterally and reacted promptly to light and accommodation. Funduscopic examination was negative. The inferior two-thirds of the left tympanic membrane was absent, and the ossicles were visible at the medial end of the canal. The right tympanic membrane was intact. A fullness of the neck was noted but definite thyroid tissue was

not palpable. The chest was symmetrical and respiratory excursions were unimpaired. The lungs were clear to auscultation and percussion, although a questionable coarse friction rub was present in the region of the left chest. Examination of the heart revealed split second aortic and pulmonic sounds. No thrill or murmur was noted. The rhythm was regular. There was no evidence of cardiac enlargement. Blood pressure was 110 mm. Hg systolic and 90 mm. diastolic; pulse, 100 per minute. Examination of the abdomen, rectum and genitalia was not remarkable. A small firm nodule, 2 to 3 mm. in diameter, was noted on the lateral aspect of the right prostatic lobe. This was later interpreted by the urologist to be a calcified prostatic nodule. No gross lymphadenopathy was found, although a few shotty nodes were felt in the inguinal regions. Neurologic examination was essentially normal.

During the subsequent prolonged hospitalization a large quantity of laboratory data was accumulated. Repeated blood counts showed a persistent leukocytosis,

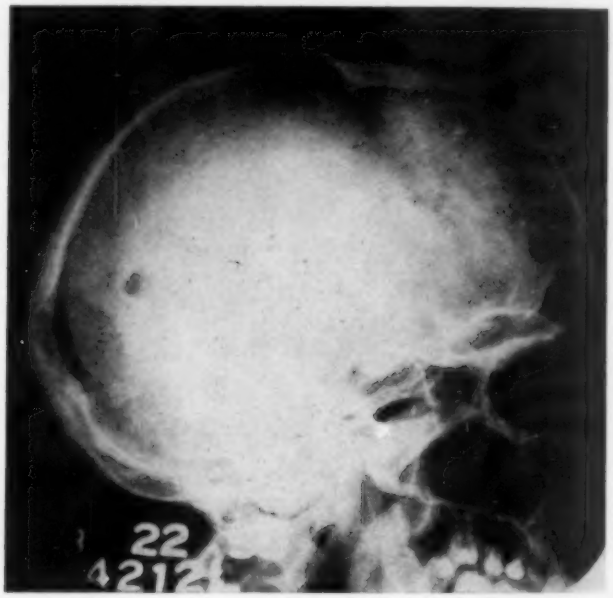


FIG. 2. Osteolytic defect in left posterior parietal region.

ranging from 9,000 to 15,000 per cm. Eosinophils varied from 2 to 10 per cent. Sternal marrow showed a regular distribution of all hemopoietic constituents and no foreign or abnormal cells. Numerous urinalyses were negative except for a persistently low specific gravity, 1.001 to 1.003. Serologic reaction for syphilis was negative. Numerous other determinations, including blood urea nitrogen, total proteins, serum calcium, sodium, potassium, cholesterol and blood sugar, were again found to be within normal limits. A Fishberg concentration test produced a maximal specific gravity of 1.005. Urea clearance was within normal limits. Basal metabolic rate was also reported to be normal. Reëxamination of sputums for acid-fast organisms and fungi was negative. Roentgenograms of the skull and a complete skeletal roentgen-ray survey showed no bone changes. Roentgenograms of the chest exhibited the same generalized pulmonary interstitial fibrosis noted previously. The electrocardiogram was normal.

Approximately 14 days after admission, while various diagnostic procedures were being undertaken, the patient noticed sudden onset of severe right chest pain following a paroxysm of coughing. He was found to have a right pneumothorax. Five hundred centimeters of air were removed from the right chest, with subsequent gradual reëxpansion of the lung. On January 20, 1950, a second spontaneous

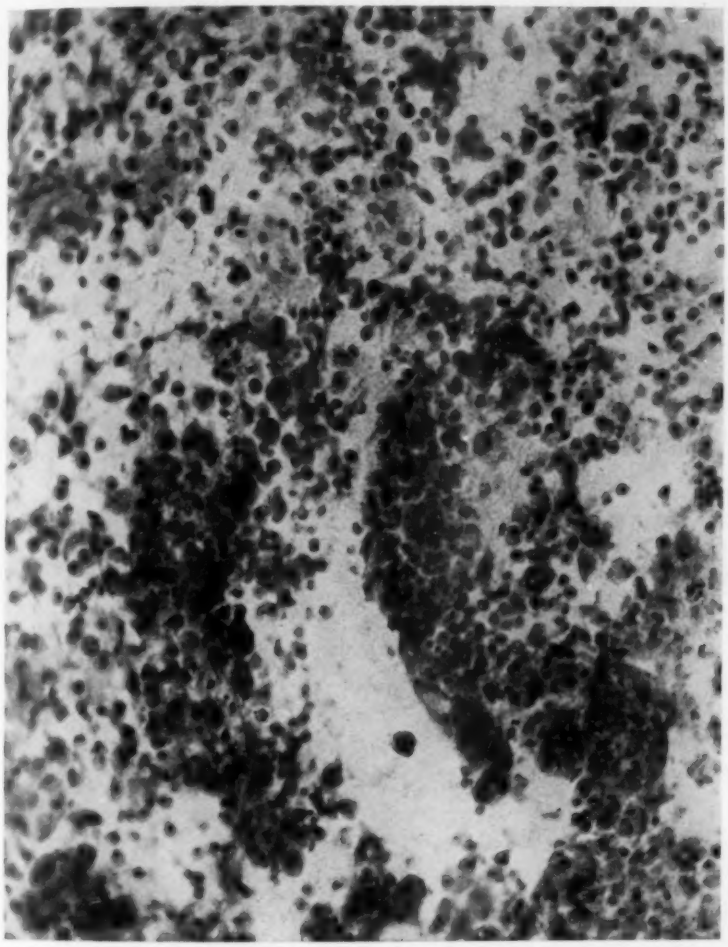


FIG. 3. Microscopic section of skull biopsy, showing a destructive granulomatous lesion resembling an eosinophilic granuloma. The concentrated dark cells are eosinophils; the pale cells are histiocytes.

pneumothorax occurred, involving the same lung. The patient was subsequently transferred to the chest service, where it was necessary to make frequent withdrawals of air from the right chest. Furthermore, he required multiple daily injections of pitressin tannate in oil to control his excessive urine volume. By February 10 there was complete reëxpansion of the involved lung. During this latter episode the patient exhibited a moderately severe urticarial reaction to a narcotic injection. On

April 10 he began to complain of severe pain in the left posterior parietal region of the skull. A roentgenogram taken at this time (figure 2) revealed an osteolytic defect in this region. A skull biopsy (figure 3) was done several days later. The pathologic lesion reported was a "destructive granulomatous lesion in the calvarium resembling an eosinophilic granuloma . . ., compatible with the clinical diagnosis of Schüller-Christian disease."

It was decided to attempt a trial course of adrenocorticotropic hormone (ACTH). The patient received a 20 mg. intramuscular injection on May 15. Approximately 20 minutes after the injection he developed a marked erythema with generalized urticaria. He became markedly dyspneic and manifested asthmatic râles. There was moderate swelling of the eyes, lips and hands. The pulse rate rose to 200 per minute.

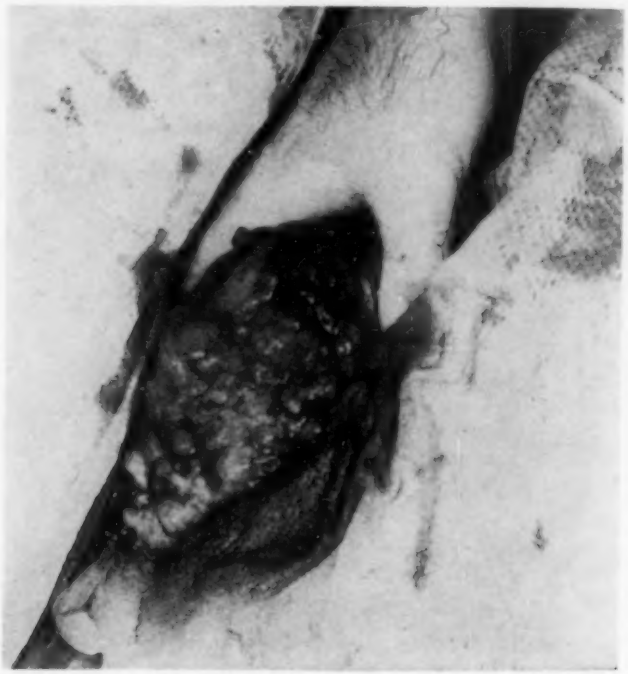


FIG. 4. The right lung, exposed during thoracotomy, exhibits far advanced pulmonary fibrosis with bullous emphysema.

This reaction subsided somewhat after the administration of 10 mg. of benadryl intravenously, and completely disappeared within 24 hours.

On May 23, intramuscular injections of 17-hydroxy, 11-dehydrocorticosterone (cortisone) were begun in gradually increasing doses to a maximum of 150 mg. a day. The greater portion of therapy was conducted at this dosage level. Pitressin tannate injections were maintained at 0.5 c.c. twice a day during the entire course of therapy. The patient noted a significant subjective improvement soon after the beginning of cortisone administration. Large irregular fluctuations began to occur in the specific gravity and volume of the urine. The specific gravity reached 1.020 or 1.030 on occasions, with corresponding decreases in urine volume, in contrast to the consistently low specific gravity and high urine volume maintained before therapy. A decrease in circulating eosinophils also occurred.

Approximately 10 days after the beginning of therapy the patient developed moderate peripheral edema, a palpable liver, questionable shifting dullness, tenderness in both flanks and moderately severe dyspnea and orthopnea. These symptoms were associated with a 10 pound gain in weight. Serum sodium at that time was reported as 321 mg. per cent (139 mEq.). Twenty-four hour urinary sodium excretion was

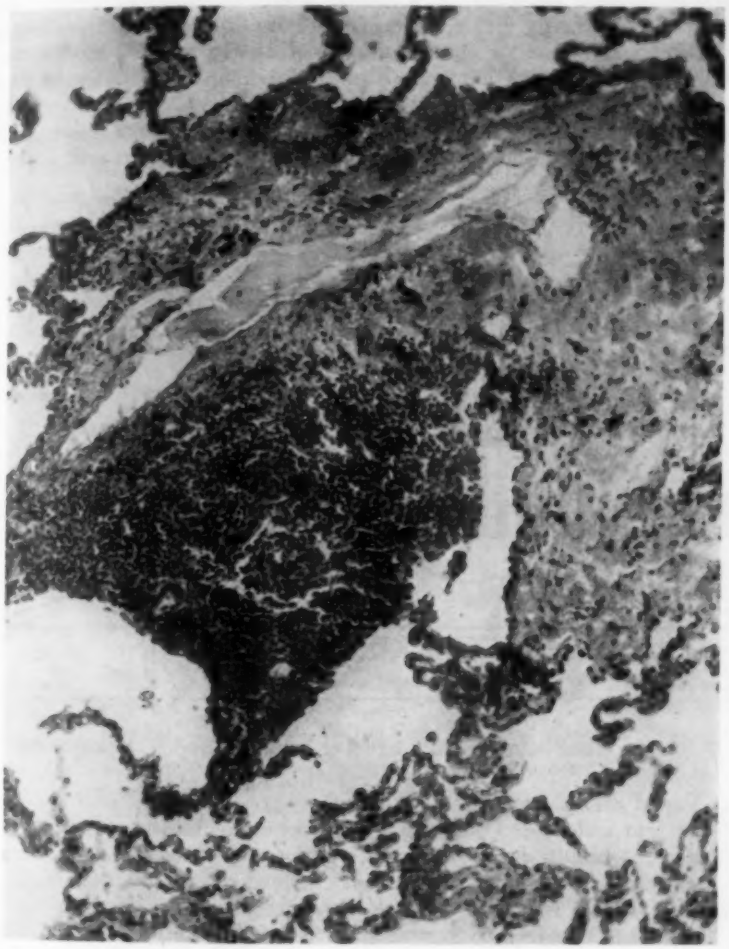


FIG. 5. Microscopic section of the right lung, showing thickening of the alveolar walls and interstitial septa as the result of focal infiltrations of histiocytes, plasma cells and eosinophils.

0.7 gm. (30 mEq.). Roentgenogram of the chest showed no change, and flat plate of the abdomen was negative. The patient was subsequently given an 800 mg. sodium diet, after which there was gradual disappearance of edema and alleviation of dyspnea and orthopnea.

On June 14, 23 days after the beginning of therapy, the patient again suffered a sudden spontaneous right pneumothorax, from which he again gradually recovered.

Cortisone was discontinued on June 20. Subjectively the patient noted a gradual and progressive decline in well-being and a diminution of energy and vigor. A prompt but gradual loss of weight occurred, with a return to pretreatment levels within one week. Fasting blood sugar, which toward the end of cortisone administration had become depressed to 34 mg. per cent (true glucose method of Kingsley and Reinhold [11]), remained depressed for approximately 30 days. Depression of circulating eosinophils persisted for a similar length of time. Large irregular fluctuations in specific gravity and volume of the urine also continued for a prolonged period. Roentgenogram of the chest at the end of the above course of therapy showed no significant change in the bilateral parenchymal infiltration. Another roentgenogram of the skull, however, showed some questionable progression of the above-described lytic lesion. On July 25 another biopsy of the original lesion in the skull was done and was reported to show "one small residual focus of lesional tissue heavily permeated by eosinophils."

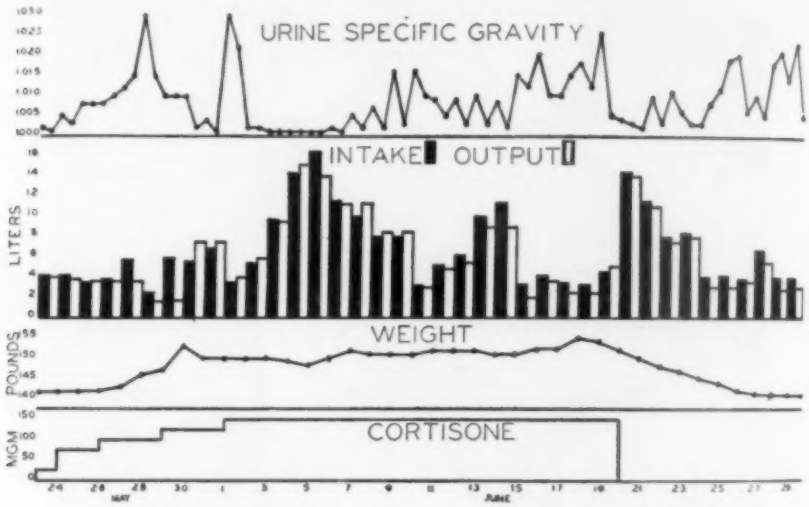


FIG. 6. Observations made during the administration of cortisone.

On August 8 he again suffered a spontaneous pneumothorax of the right lung with 60 per cent collapse. Following several unsuccessful attempts to reëxpand the right lung, a thoracotomy was performed. At operation the right lung was seen to exhibit far advanced pulmonary fibrosis with bullous emphysema (figure 4). Biopsy of the lung (figure 5) revealed "thickening and vascularization of the pleura, thickening of the alveolar walls and interstitial septa from scarring and infiltration by histiocytes and inflammatory cells, including plasma cells and some eosinophils. Occasional conversion of histiocytic cells to lipophages. . . . Altogether, the changes are those observed in Schüller-Christian's disease which is still in progress." Following operation the patient made a very slow and tedious recovery, with gradual and progressive reëxpansion of the right lung. As soon as was reasonably feasible, radiation therapy was begun and is now in progress.

COMMENT

The interesting progression of symptoms in this case deserves further comment. From the history, it would not be too presumptive to assume that mastoid

involvement, and subsequent persistent middle ear infection, may have been the earliest manifestation of the disease. The occurrence of lymphadenopathy in the early stages is also a relatively common but often obscure finding. According to some writers, however, the development of extensive pulmonary fibrosis is unusual.[12] Lichtenstein, on the contrary, believes it to be a frequent complication, particularly in adults, which sometimes leads to cor pulmonale and congestive heart failure. Frequent spontaneous pneumothoraces are likewise a common occurrence.[13]

The classic triad of exophthalmos, diabetes insipidus and skull defects is not essential for the diagnosis of Hand-Schüller-Christian's syndrome. One may observe each symptom alone or in various combinations. The finding of an osteolytic long bone or calvarial defect associated with unexplained bilateral pulmonary fibrosis should suggest Hand-Schüller-Christian's syndrome. Furthermore, the biopsy of such a bone lesion may be the only means of differentiating this syndrome from Boeck's sarcoid.[14]

The early diagnosis is not entirely of academic interest, since an efficacious therapeutic measure is available, notably deep roentgen-ray therapy. Because of the gradual fibroblastic transformation of the granulomatous lesions, early therapy should be most effective. Imler [15] and Currens and Popp [16] report satisfactory therapeutic response in osseous lesions with moderate doses of roentgen-ray, and similar success has been noted with lymphatic lesions. The roentgen-ray treatment of skin and visceral lesions, on the other hand, has been much less encouraging. Dietary measures such as the low fat diet suggested by Rowland [5] are of no value.

In view of the uncertain benefits of radiation therapy in visceral involvement and its marked fibroblastic tendency, the need for a better therapeutic agent is apparent. Because of its inhibitory effect on fibroblastic proliferation,[17] as well as its anti-allergic and eosinophil depressant properties,[18] a trial course of ACTH was undertaken. It was necessary to abandon this therapy immediately, however, because of a severe anaphylactoid reaction which occurred after the administration of the first dose. In retrospect, the possibility of such a reaction might have been suspected in an individual with an allergic diathesis. The patient's cutaneous sensitivity to ACTH was pronounced at dilutions of 1:1,000,000. Similar allergic reaction to ACTH, apparently related to a specific porcine sensitivity, has been observed by one of us (S. H. B.).

In view of the discouraging results with ACTH, it was decided to attempt further therapy with cortisone. The initial response to cortisone was quite satisfactory and was manifested by subjective well-being, markedly increased appetite and a fall in circulating eosinophils. Further evidence of cortisone effect was the appearance of peripheral edema, dyspnea and weight gain, with sodium retention despite a tremendous daily urinary output which rose on occasions to 16 L. (figure 6). The most significant physiologic change was the striking fluctuation in specific gravity of the urine which occurred at irregular intervals during therapy. Furthermore, a definite inverse relationship was seen between the specific gravity and the urine volume.

Upon the completion of cortisone therapy there was a prompt but gradual loss of weight (figure 6) and a subjective decline in well-being. This weight loss was not associated with a significant diuresis and may possibly be attributed to the

marked progressive diminution in appetite which occurred. Depression of circulating eosinophils and blood sugar persisted for approximately four weeks. There were repeated irregular two- to six-day periods during which the specific gravity of the urine remained high and the urine volume low. A post-treatment biopsy of the skull at the original site showed one small remaining presumably active focal lesion. There was, however, no evidence of further development of the original skull lesion and no indication of new osseous lesions.

In view of the side reactions and equivocal results obtained with cortisone, therapy over a longer term or in higher dosage did not seem advisable. Radiation therapy was subsequently instituted and is currently in progress.

Summary

A case of Hand-Schüller-Christian's syndrome in an adult patient is presented. The nature and manifestations of this condition, which are only occasionally observed in the adult, are described. The importance of early diagnosis and radiation therapy is indicated. A therapeutic trial with ACTH and cortisone is reported in detail.

Addendum

Since the acceptance of this article for publication, the patient completed a two months' course of radiation therapy. Roentgenograms revealed no change in the skull or pulmonary lesions; the symptoms of diabetes insipidus persisted. There has been subsequently, a gradual deterioration of the patient's condition. He has been plagued by a series of severe respiratory infections and another spontaneous pneumothorax of the left lung. In final desperation, cortisone was again instituted. The general condition of the patient has been relatively improved by this therapy, but there is still no evidence of regression of the underlying disease process.

BIBLIOGRAPHY

1. Hand, A.: General tuberculosis, Proc. Path. Soc. Philadelphia **16**: 282, 1891–1893.
2. Kay, T. W.: Acquired hydrocephalus with atrophic bone changes, exophthalmos and polyuria, Pennsylvania M. J. **9**: 520, 1905–1906.
3. Schüller, A.: Dysostosis hypophysaria, Brit. J. Radiol. **31**: 156, 1926.
4. Christian, H. A.: Defects in membranous bones, exophthalmos and diabetes insipidus; an unusual syndrome of dyspituitarism, M. Clin. North America **3**: 849, 1920.
5. Rowland, R. S.: Xanthomatosis and reticulo-endothelial system, Arch. Int. Med. **42**: 611, 1928.
6. Thannhauser, S. J., and Magendantz, H.: The different clinical groups of xanthomatous diseases; a clinical physiological study of 22 cases, Ann. Int. Med. **11**: 1662, 1938.
7. Holm, J. E., Teilum, G., and Christensen, E.: Eosinophilic granuloma of bone; Schüller-Christian disease, Acta med. Scandinav. **118**: 292, 1944.
8. Jaffe, H. L., and Lichtenstein, L.: Eosinophilic granuloma of bone; a condition affecting one, several or many bones, but apparently limited to the skeleton, and representing the mildest clinical expression of peculiar inflammatory histiocytosis also underlying Letterer-Siwe disease and Schüller-Christian disease, Arch. Path. **37**: 99, 1944.
9. Farber, S.: The nature of "solitary or eosinophilic granuloma" of bone, Am. J. Path. **18**: 625, 1941.
10. Thannhauser, S. J.: Lipidoses, 1949, Oxford University Press, New York.
11. Kingsley, G. R., and Reinhold, J. G.: The determination of true glucose in blood by reduction of ferricyanide, J. Lab. and Clin. Med. **34**: 713, 1949.

12. Schneirerson, S. J., and Schneider, L.: Lipoid granulomatosis (xanthomatosis) with marked pulmonary fibrosis and cor pulmonale, Ann. Int. Med. **30**: 842, 1949.
13. Lichtenstein, L.: Personal communication.
14. Freiman, D. G.: Medical progress: sarcoidosis, New England J. Med. **239**: 664 (Oct. 28); **239**: 709 (Nov. 4); **239**: 743 (Nov. 11) 1948.
15. Imler, A. E.: Reticulo-endotheliosis with report of two cases, Am. J. Roentgenol. **56**: 343, 1946.
16. Currens, J. H., and Popp, W. C.: Xanthomatosis, Hand-Schüller-Christian type; report of a case with pulmonary fibrosis, Am. J. M. Sc. **205**: 780, 1943.
17. Ragan, C., Howes, E. L., Plotz, C. M., Meyer, K., Blunt, J. W., and Lattes, R.: The effect of ACTH and cortisone on connective tissue, Bull. New York Acad. Med. **26**: 251, 1950.
18. Fischel, E. E.: The relationship of adrenal cortical activity to immune responses, Bull. New York Acad. Med. **26**: 255, 1950.

EDITORIAL

LIPIDS AND ATHEROSCLEROSIS

ALTHOUGH some 40 years have elapsed since Windaus [1] reported the predominance of cholesterol and its esters in human atherosclerotic lesions and Anitschkow [2] produced experimental atherosclerosis in the rabbit by the feeding of cholesterol, an etiological hypothesis, capable of verification at every step, is still a matter of the future. Experimental investigation at present is quite active and is no longer hampered by the dictum that human atherosclerosis is an inevitable concomitant of the process of aging. The volume of investigations dealing with the relationship of lipid metabolism to atherosclerosis has reached staggering proportions, but the results are still controversial. Recently new links have been added to the chain of circumstantial evidence connecting the two which are of considerable interest.

The study of human atherosclerosis has always been hampered by the paucity of diagnostic clinical criteria prior to the occurrence of some serious overt consequence of the disease. Even today one still encounters fallacious clinical inferences based upon the finding of rigid, thickened, "pipestem" peripheral arteries characteristic of medial (Monckeberg's) sclerosis, an entity quite apart from intimal atherosclerosis. Although most cases occur in individuals without obvious disturbances of lipid metabolism, the greater incidence and extent of atherosclerosis in such diseases as diabetes mellitus, hypothyroidism, the nephrotic syndrome, xanthomatosis, etc. has been too striking to be overlooked.[3] Major emphasis has usually been placed upon the hypercholesterolemia which is a common feature of these entities. Cholesterol, in common with other lipids in the serum, occurs only in the form of large, molecular colloidal aggregates or micellae.[4] The chemical methods commonly employed to quantitate these substances destroy the giant lipid molecules and give no information regarding their physico-chemical state. Recent investigations suggest that the physical state of the lipids in the blood may be of as great, or greater, significance in the etiology of atherosclerosis as their actual quantity.

Ingested fat is emulsified and partially hydrolyzed in the small intestine prior to absorption. Frazer [5] states that hydrolysis by pancreatic lipase is incomplete and that absorption occurs by several pathways. Unhydrolyzed neutral fat may be emulsified and absorbed as such from the intestine.

[1] Windaus, A.: Ueber den Gehalt normalen und atheromatosen Aorten an Cholesterin und Cholesterinestern, Ztschr. f. physiol. Chem. **67**: 174, 1910.

[2] Anitschkow, N.: Experimental atherosclerosis in animals, Chapter 10 *in* Arteriosclerosis, E. V. Cowdry, ed., 1933, The Macmillan Co., N. Y.

[3] Gubner, R., and Ungerleider, H. E.: Arteriosclerosis: a statement of the problem. Am. J. Med. **6**: 60, 1949.

[4] Blix, G., Tiselius, A., and Svensson, H.: Lipids and polysaccharides in electrophoretically separated blood serum proteins, J. Biol. Chem. **137**: 485, 1941.

[5] Frazer, A. C.: The absorption of triglyceride fat from the intestine, Physiol. Rev. **26**: 104, 1946.

The pathway is via the lacteals and thoracic duct to the systemic circulation and thence to fat depots. The fatty acids liberated by hydrolysis in the intestines are absorbed and transported by the portal circulation to the liver. This is the so-called partition theory of fat absorption. The factors determining the different pathways are not yet clear. Frazer has suggested that the physical state of the material may be of significance in this regard. Emulsified neutral fat is absorbed in particulate forms of 0.5 micron or less in diameter, whereas the fatty acids are in the molecular state as a water-soluble complex.

It is well known that following the absorption of a fatty meal a variable period of lipemia occurs, during which the serum has a turbid, "milky" appearance in contrast to its clarity in the fasting state. Gage and Fish,[6] in 1924, first applied the term, chylomicrons, to the large visible particles which they observed, with the dark field microscope, suspended in the serum during the period of alimentary lipemia. Frazer and his coworkers [7] extended these observations and demonstrated the lipid nature of the particles. They also concluded that a layer of globulin was present at the oil-water interface of the colloidal suspension. Particles of various sizes could be seen ranging from very bright ones with an approximate diameter of one micron to small, dull ones with a diameter of 35 millimicrons. These investigators studied variations in fat absorption after a fat-rich meal. Chylomicron counts were made before and after the meal and a curve, the chylomicrograph, plotted. Considerable normal variation was observed.

In the fasting state the clarity of the serum is due to the fact that almost all the lipid occurs in a highly dispersed, ultramicroscopic colloidal state. Apart from neutral fat, the content of which varies with relation to fat ingestion and absorption, the lipid components of serum are almost evenly divided between a cholesterol fraction and a phospholipid fraction.[8] As is well known, the cholesterol fraction consists of a free and an esterified portion, the latter constituting approximately 75 per cent of the total. The phospholipid fraction is largely composed of lecithin, with smaller increments of cephalin and sphingomyelin. Both lecithin and cholesterol are concerned with fatty acid transport. The fatty acid-cholesterol esters are hydrophobic and insoluble and are maintained in colloidal "solution" by the hydrophilic phospholipid esters. Lecithin has been known for many years as a "stabilizer" of oil in water emulsions. Recent work has further substantiated the fact that almost all the lipid of human plasma exists in the form of a lipoprotein complex with the lipid in loose combination with alpha and beta globulin. The stability of these colloidal aggregates can be altered in various ways.

[6] Gage, S. H., and Fish, P. A.: Fat digestion, absorption and assimilation in man and animals as determined by the dark field microscope and a fat-soluble dye, Am. J. Anat. **34**: 1, 1924.

[7] Elkes, J. J., Frazer, A. C., and Stewart, H. C.: The composition of particles seen in normal human blood under dark-ground illumination, J. Physiol. **95**: 68, 1939.

[8] Thannhauser, S. J.: Serum lipids and their value in diagnosis, N. Eng. J. Med. **237**: 515, 1947.

In a recent study Ahrens and Kunkel [9] called attention to the importance of the phospholipids in the stabilization of serum lipid emulsions. Some sera with a high total lipid content may be perfectly clear whereas others with similar or even lesser lipid content will be quite turbid or "milky." The physical difference between the two types lies in the lipid particle size. Particles with diameters less than one-quarter the wave length of visible light (or 0.1 micron) will not be seen in the visible light range and the containing serum will be clear, whereas larger particles by interrupting light rays give the serum the appearance of turbidity. Analysis of such pairs of sera demonstrated that the important difference lay in the phospholipid: total lipid ratio. For example, a serum containing 2,969 mg. of total lipid, of which 1,400 mg. was phospholipid (ratio — 0.47), was quite clear in contrast to another, markedly turbid, in which the total lipid content was only 1,128 mg. and the phospholipid, 312 mg. (ratio — 0.28). A clear high lipid serum could be made turbid by destroying the lecithin with lecithinase. It was not possible, in vitro, to increase the clarity of milky serum by increasing its phospholipid content.

The possible relationship of this physico-chemical phenomenon to the pathogenesis of atherosclerosis has been stressed in several recent studies. Kellner et al.[10] found that cholesterol-fed rabbits which also received intravenous injections of the surface-active agents Tween 80 and Triton A20 developed a sustained hypercholesterolemia and yet failed to develop as great a degree of atherosclerosis as those animals receiving only cholesterol. Chemical analysis revealed that the former group had a proportional rise of both cholesterol and phospholipid, while the latter showed a disproportionate increase of cholesterol. Duff and Payne [11] found that the hypercholesterolemia of alloxan diabetic rabbits was not associated with as great a degree of atherosclerosis as was to be expected. In addition to hypercholesterolemia, these animals also exhibited a marked elevation of phospholipid and neutral fat. Gertler, Garn, and Lerman [12] studied lipid inter-relationships in a group of 97 patients with coronary heart disease and in two control groups. They found not only a significantly elevated mean cholesterol level in the former group but also an increase in the cholesterol: phospholipid ratio due to a disproportionate rise in cholesterol.

The investigations thus far cited, as well as others to be mentioned below, are of interest for several reasons. First, they focus attention upon an abnormality of lipid metabolism or transport which additional studies

[9] Ahrens, E. H., and Kunkel, H. G.: The stabilization of serum lipid emulsions by serum phospholipids, J. Exper. Med. **90**: 409, 1949.

[10] Kellner, A., Correll, J. W., and Ladd, A. T.: The influence of intravenously administered surface-active agents on the development of experimental atherosclerosis in rabbits, J. Exper. Med. **93**: 385, 1951.

[11] Duff, G. L., and Payne, T. F. B.: The effect of alloxan diabetes on experimental cholesterol atherosclerosis in the rabbit. III. The mechanisms of the inhibition of experimental cholesterol atherosclerosis in alloxan-diabetic rabbits, J. Exper. Med. 92: 299, 1950.

[12] Gertler, M. M., Garn, S. M., and Lerman, J.: The interrelationships of serum cholesterol, cholesterol esters and phospholipids in health and in coronary artery disease, Circulation **2**: 205, 1950.

may reveal as characteristic of the individual developing atherosclerosis. Secondly, they revive interest in the relationship of macromolecules to the development of this disease. It is well known that the aorta, and presumably other arteries, shows an increasing accumulation of lipids with advancing age. These lipids are of the same type, but not necessarily in the same proportions, as those found in the serum. A recent study [13] has shown that the "normal" age-conditioned accumulation of lipids is largely due to an increase of these substances in the media. Atherosclerotic lesions add even a greater increment of lipids predominantly localized in the intima. The quantity of lipid is so large as to preclude the possibility of it's origin from the simple breakdown of tissue in the intima, but suggest that it must be brought from without and deposited. Pathological studies suggest that both experimental and human atherosclerosis develops in an episodic fashion. This is exemplified by the finding of lesions, often side by side, which are characteristic of the earliest as well as the most advanced phases of the disease. Hueper [14] suggested that a disturbance in the colloidal stability of the serum lipids may result in deposition of a film of macromolecules on the endothelium with resultant interference with oxgenation of these cells. Anoxia leads to increased permeability of the intimal membrane and the deposition of lipid-laden cells in the intima. In support of this hypothesis, Hueper produced lesions resembling experimental cholesterol and human atherosclerosis by the injection of a variety of macromolecular colloidal carbohydrates such as polyvinyl alcohol, methyl cellulose, pectin, and acacia. The macrophages in the intimal lesions contained these substances. Moreton [15] has suggested that the recurrent hyper- and macrochylomicronemia observed after fat-rich meals may be responsible for the development of atherosclerosis. Zinn and Griffith [16] concluded from a study of lipomicrons (any fat particle) in the sera of individuals in the fasting state that there was a significantly higher proportion of chylomicrons (large fat particles) in patients with proved atherosclerosis as compared to normals. In 1943, Hahn [17] demonstrated that the intravenous injection of heparin increased the translucence of plasma during the period of alimentary lipemia. The change was considered to be due to a purely physical effect upon the lipo-protein complex. Block et al.[18] have recently studied this phenomenon in a group of 27 patients with proved atherosclerosis and a group of controls. Following a standard fat meal heparin was administered

[13] Buck, R. C., and Rossiter, R. J.: Lipids of normal and atherosclerotic aortas: a chemical study, Arch. Path. **51**: 224, 1951.

[14] Hueper, W. C.: Arteriosclerosis, a general review, Arch. Path. **39**: 51, 1945.

[15] Moreton, J. R.: Chylomicronemia, fat tolerance, and atherosclerosis, J. Lab. and Clin. Med. **35**: 373, 1950.

[16] Zinn, W. J., and Griffith, G. C.: A study of serum fat globules in atherosclerotic and non-atherosclerotic male subjects, Am. J. M. Sc. **220**: 597, 1950.

[17] Hahn, P. F.: Abolishment of alimentary lipemia following injection of heparin, Science **98**: 19, 1943.

[18] Block, W. J., Jr., Vann, F. D., and Barker, N. W.: Effect of small doses of heparin in increasing the translucence of plasma during alimentary lipemia: Studies in normal individuals and patients with atherosclerosis, Proc. Staff Meet., Mayo Clin. **26**: 246, 1951.

and the effect upon translucence of the serum noted by spectrophotometry. The atherosclerotic group showed an average clearing of only 38 per cent as compared to 74 per cent in the normal males. The possibility was suggested that the difference might be due to a basic abnormality in the state of the plasma lipids.

Perhaps the most exact study of this problem, thus far, is that of Gofman and his coworkers.[19] The ultracentrifuge capable of producing forces many thousands or millions of times the force of gravity was employed to study the character and behavior of the giant lipo-protein molecules present in the sera of normal individuals as well as in patients with coronary artery disease, hypothyroidism, diabetes, hypertension, the nephrotic syndrome, and cholesterol-fed rabbits. The technic as well as the terminology requires some elucidation. When subjected to forces of the dimension produced in an ultracentrifuge, molecules dispersed in a solution will either sediment, if heavier than the solution, or float if lighter than the solution. The unit of migration is the Svedberg (S) and sedimentation or flotation is indicated by the use of the first letter of the respective words. In these experiments flotation occurred; therefore the molecules were classified in Sf units. The rate of flotation (or sedimentation) is a physical constant of the molecular species under the given conditions of the experiment. A special optical device permitted photographs to be made of the rate and extent of migration. Quantitation of the amount of a given molecular species was possible from these graphs.

Four classes of molecules were found in human sera: 1. Molecules with an Sf value greater than 75. This group included the chylomicrons mentioned above. Their concentration increased during alimentary lipemia. No correlation between their occurrence and clinical evidence of atherosclerosis could be obtained. 2. Molecules with Sf values of 30–70 which appeared to have no pathogenic significance. 3. Molecules of Sf 10–20 class which seemed definitely correlated with the presence of atherosclerosis. These molecules were composed of approximately 30 per cent cholesterol. 4. Molecules of the Sf 3–8 class are present in all sera and carry a major portion of serum cholesterol, phospholipid and protein. They are apparently unrelated to atherosclerosis.

The sera of cholesterol-fed rabbits contained two other classes of molecules analogous to certain of the human groups noted above. With continuation of the period of cholesterol feeding molecules of the Sf 5–8 class (equivalent to human Sf 3–8 group) reached a maximum, following which molecules of the Sf 10–30 class (equivalent to human group Sf 10–20) appeared in increasing concentration. Some rabbits did not demonstrate the latter group. Animals were autopsied at the end of a 15 week period of study. The degree of atherosclerosis was found to be proportional to the concentration of Sf 10–30 molecules. In another experiment the simul-

[19] Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A., and Strisower, B.: Blood lipids and human atherosclerosis, Circulation 2: 161, 1950.

taneous feeding of cholesterol and potassium iodide resulted in a lesser concentration of Sf 10–30 molecules and a correspondingly lesser degree of atherosclerosis.

The presence of Sf 10–20 molecules in a proportion of the normal human controls was felt to be compatible with the concept that in any "normal" population a certain percentage are individuals who are developing atherosclerosis, but have no overt manifestations yet. Obviously long term follow up of such individuals is indicated. In a group of 252 patients who had had an episode of myocardial infarction, over 90 per cent showed Sf 10–20 molecules in concentrations greater than seen in the normal group. Similar findings were observed in the diabetics, hypertensives, and hypothyroids. The highest concentrations of these molecules were found in four patients with the nephrotic syndrome. One, a six year old child, showed extensive atherosclerosis of the abdominal aorta at autopsy. The correlation between the concentration of Sf 10–20 molecules in a serum and its cholesterol content was poor, although those with quite high cholesterol levels tended to show an increase in concentration of these molecules. A single fat-rich meal did not affect their concentration although the larger molecules were transiently increased.

Certain interesting observations were made on the influence of diet on the concentration of Sf 10–20 molecules. A very careful dietary history in 43 individuals failed to reveal any definite correlation between the previous intake of fat and cholesterol and the level of Sf 10–20 molecules. This was interpreted as reflecting the wide variation in fat tolerance which exists in the population. However, it was noteworthy that both patients and normals maintained on a low fat-low cholesterol diet uniformly showed a decrease in the concentration of these molecules. Upon relaxation of the dietary restrictions their concentration increased.

The development of human atherosclerosis undoubtedly represents the interaction of many factors. Certain contributing or secondary factors such as hypertension, luetic aortitis, and rheumatic arteritis can without hesitation be incriminated. The investigations cited above seem to link, even more closely, abnormal lipid metabolism and atherosclerosis. Further investigation of the physico-chemical state of the serum lipids should result in a far greater insight into the problem than was ever possible from the narrow study of cholesterol metabolism. At present only the most empirical concepts of therapy and prevention can be extracted from existing data. Interpretations of the efficacy of any therapeutic regimen can only be based upon rigidly controlled studies. It is not unreasonable to expect real progress in understanding and control of this tremendous problem in the near future.

MILTON S. SACKS, M.D.

REVIEWS

A Textbook of Medicine. 8th Ed. Edited by RUSSELL L. CECIL, M.D., Sc.D., and ROBERT F. LOEB, M.D. 1,627 pages; 18 × 26 cm. W. B. Saunders Company, Philadelphia. 1951. Price, $12.00.

In this era of expanding universes and textbooks, it is indeed a joy to find that skilful editing has actually reduced this standard text in its latest edition by over one hundred pages.

For this edition Dr. Cecil has been joined by Dr. Robert Loeb as Co-Editor, and the services of Drs. Alexander Gutman, Walsh McDermott and Harold Wolff have been secured as Associate Editors. Owing to the death or retirement of a number of former contributors, some 80 treatises have been recast. A number of articles on subjects not dealt with in previous editions have been added: these subjects include Q fever, rickettsialpox, *H. influenzae* infections, Clostridium infections, pinta, urticaria, an introduction to diseases of collagen, carbon tetrachloride poisoning, chronic amphetamine poisoning, vitamin B–12 deficiency, folic acid deficiency, inborn errors of metabolism, amyloidosis, pulmonary function in health and disease, renal physiology and tests of renal function, toxemia of pregnancy, fibrous dysplasia of bone, tumors of bone and phenylpyruvic oligophrenia.

In line with modern trends the authors in this edition have laid special stress on the physiological, biochemical and psychological aspects of disease. It is satisfactory to find adequate coverage of a number of syndromes which are well established, yet sometimes ignored in other textbooks, such as hypersplenism, primary amyloidosis and focal nephritis. The text, as usual, is excellent for the student, but, on the whole, too sketchy for the internist's every need. It is probably true to say, however, that it fills the requirements of the practitioner of internal medicine as well as any single volume can. Criticisms of the text are limited to minor points and need not be recorded in detail.

Cecil's *Textbook of Medicine* is so well and so universally known that a review of a new edition seems almost superfluous. The same attractive format has been retained, and the new sections are well up to the general standard of the text. It remains the best standard work of its kind by American authors.

H. J. L. M.

Problems of Infancy and Childhood: Transactions of the Fourth Conference, March 6–7, 1950, New York. Edited by MILTON J. E. SENN, M.D. 181 pages; 15.5 × 23.5 cm. Sponsored and published by the Josiah Macy, Jr. Foundation, New York. 1951. Price, $2.25.

This book represents one of a series, presenting round table discussions, organized by the Josiah Macy, Jr. Foundation, for the purpose of gathering material in preparation for the Midcentury White House Conference on Children and Youth which was held in Washington December 1950. The text consists essentially of three parts. In the first part two prominent anthropologists, Dr. George P. Murdock of Yale and Dr. John W. M. Whiting of Harvard, present a joint study entitled "Cultural Determination of Parental Attitudes; The Relationship between the Social Structure, Particularly Family Structure and Parental Behavior." In the second part, Dr. Theodore C. Schneirla, of the American Museum of Natural History, presents a paper on "A Consideration of Some Problems in the Ontogeny of Family Life and Social Adjustment in Various Infrahuman Animals." In the third part Dr. Lawrence K. Frank, a social scientist, presents a paper entitled "Working toward Healthy

Personality." Each of these presentations is followed by the verbatim account of the discussion of a mixed panel consisting of prominent pediatricians, psychiatrists, sociologists and anthropologists. Although the discussions are quite confusing, the three presentations are excellent. In the first, one gets a clear picture of modern research methods in the field of anthropology. In the second one finds a clear description of a biologist's approach to the questions of instincts and social life of animals. In the third one finds some highly provocative suggestions regarding methods of rearing children in our culture. As can be observed, the title "Problems of Infancy and Childhood" is a bit misleading, since little real light is thrown on the common problems of childhood. The book is worth reading for the sake of the three main studies presented.

H. W. N.

Clinical Heart Disease. 4th Ed. By SAMUEL A. LEVINE, M.D., F.A.C.P., Clinical Professor of Medicine, Harvard Medical School. 556 pages; 16.5 × 25.5 cm. W. B. Saunders Co., Philadelphia. 1951. Price, $7.75.

This is the most recent edition of an already established textbook in clinical heart disease. The author, as in previous editions, stresses the clinical resources available to the physician in making a diagnosis. He does not intend to be encyclopedic. He discusses the various important types of heart disease, emphasizing "that information which is directly helpful in the care of the patient." There is an enlarged and revised section on electrocardiography.

This is a personalized text, reflecting the author's opinion, devoid of bibliographic references. The personalized style is good in that it gives the practitioner a definite opinion; the lack of references is unfortunate in that it does not indicate to the intelligent reader the sources where he may seek further information. This book is clearly and interestingly written and reflects extensive experience. It is recommended to the general practitioner, for whom it is written.

S. S.

Physical Diagnosis. By RAYMOND W. BRUST, A.B., M.D., F.A.C.P., Associate in Medicine, University of Pennsylvania Medical School; introduction by TRUMAN G. SCHNABEL, A.B., M.D., F.A.C.P. 294 pages; 22 × 15 cm. Appleton-Century-Crofts, Inc., New York. 1951. Price, $4.50.

The author has designed this little book (294 pages) to be a review of the subject, complete without unnecessary detail, and avoiding the use of such related subjects as x-ray, electrocardiography and other laboratory technics. He has attempted a difficult task and in general he has succeeded. The virtues of the book exceed its deficiencies and it may be recommended as a useful undergraduate text.

T. C. W.

BOOKS RECEIVED

Books received during August are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Afecciones Endocrinas: Mecanismo de Exteriorización Clinica Orientación del Tratamiento. By EMILIO COLOMBO. 333 pages; 23 × 15 cm. (paper-bound). 1950. Lopez y Etchegoyen S. R. L., Buenos Aires.

Allergy in Relation to Pediatrics—An official publication of The American College of Allergists. By BRET RATNER, M.D., Professor of Clinical Pediatrics (Allergy)

and Associate Professor of Immunology, New York Medical College, etc.; Panel Discussion: T. N. Harris, M.D.; Ben F. Feingold, M.D.; M. Murray Peshkin, M.D.; Lewis Webb Hill, M.D.; William P. Buffum, M.D.; Edward Scott O'Keefe, M.D.; W. Ambrose McGee, M.D.; Susan C. Dees, M.D.; A. J. Horesh, M.D.; Dorothy W. Baruch, Ph.D.; Hyman Miller, M.D.; Richard H. Todd, M.D.; William C. Deamer, M.D.; James C. Overall, M.D.; Albert V. Stoesser, M.D., Ph.D., and Jerome Glaser, M.D. 228 pages; 20 × 14 cm. 1591. Bruce Publishing Company, Saint Paul, Minnesota. Price, $3.75.

Backache, Birth and Figure Relief by Self-Revolving Hipbones. By Wm. Schoenau. 264 pages; 22.5 × 14.5 cm. 1951. Wm. Schoenau, Los Angeles. Price, $2.00.

Children's Radiographic Technic. By Forrest E. Shurtleff, R.T., The Children's Medical Center, Boston. 80 pages; 26.5 × 18 cm. 1951. Lea & Febiger, Philadelphia. Price, $3.75.

Clinical Hematology. 3d ed. By Maxwell M. Wintrobe, M.D., Ph.D., Professor of Medicine and Director, Laboratory for the Study of Hereditary and Metabolic Disorders, University of Utah, College of Medicine, Salt Lake City, Utah, etc. 1048 pages; 24.5 × 15.5 cm. 1951. Lea & Febiger, Philadelphia. Price, $12.50.

A Color Atlas of Morphologic Hematology, with a Guide to Clinical Interpretation—From the Second and Fourth (Harvard) Medical Services and the Thorndike Memorial Laboratory, Boston City Hospital. By Geneva A. Daland, B.S., Chief Laboratory Assistant in Hematology, Thorndike Memorial Laboratory, etc.; edited by Thomas Hale Ham, M.D., Assistant Professor of Medicine, Harvard Medical School, etc.; illustrations by Etta Piotti. 74 pages; 28 × 21 cm. 1951. Harvard University Press, Cambridge. Price, $5.00.

Cunningham's Text-book of Anatomy. 9th ed. Edited by James Couper Brash, M.C., M.A., M.D., D.Sc., F.R.C.S. Ed., F.R.S.E., Professor of Anatomy, University of Edinburgh. 1604 pages; 26 × 16.5 cm. 1951. Oxford University Press, New York. Price, $14.00.

Diabetes Control. By Edward L. Bortz, M.D., Chief of Medical Service B, The Lankenau Hospital, etc. 264 pages; 20.5 × 14 cm. 1951. Lea & Febiger, Philadelphia. Price, $3.50.

The Early Diagnosis of the Acute Abdomen. 10th ed. By Zachary Cope, B.A., M.D., M.S. Lond., F.R.C.S. Eng., Consulting Surgeon to St. Mary's Hospital, Paddington, etc.; 270 pages; 22.5 × 14.5 cm. 1951. Oxford University Press, New York. Price, $3.50.

Experiment in Dental Care: Results of New Zealand's Use of School Dental Nurses—World Health Organization: Monograph Series. By John T. Fulton, D.D.S., Dental Services Adviser, Children's Bureau, Social Security Administration, Federal Security Agency, Washington, D.C. 87 pages; 24 × 16 cm. (paperbound). 1951. World Health Organization, Geneva. Price, $1.00.

Frontal Lobotomy and Affective Behavior: A Neurophysiological Analysis. By John F. Fulton, M.D., Sterling Professor of Physiology, Yale University. 159 pages; 21 × 14 cm. 1951. W. W. Norton & Company, Inc., New York. Price, $3.00.

Incontinence in Old People. By John C. Brocklehurst, M.D., Major R.A.M.C. Formerly Christine Hansen Research Fellow in the University of Glasgow; with a Foreword by Stanley Alstead, M.D., F.R.C.P., Regius Professor of Materia

Medica and Therapeutics, University of Glasgow. 191 pages; 25.5 × 17.5 cm. 1951. E. & S. Livingstone, Ltd., Edinburgh; agents for U. S. A.: Williams & Wilkins, Baltimore. Price, $6.50.

Lecciones de Clinica Medica: Diagnostico Diferencial. By LUIS GRAVANO. 399 pages; 23 × 16 cm. (paper-bound). 1951. Lopez y Etchegoyen, S. R. L., Buenos Aires.

Leitfaden der Laparoskopie und Gastroskopie. By H. KALK and W. BRÜHL, with the assistance of W. BURGMANN. 158 pages; 25 × 17.5 cm. 1951. George Thieme Verlag, Stuttgart. Price, Ganzleinen DM 27.–

Metabolic Methods: Clinical Procedures in the Study of Metabolic Functions. By C. FRANK CONSOLAZIO, Chief of Biochemistry, United States Army, Medical Nutrition Laboratory, Chicago; ROBERT E. JOHNSON, M.D., D.Phil. (Oxford), Professor and Head of the Department of Physiology, University of Illinois, Urbana, and EVELYN MAREK, M.A., Biochemist, United States Army, Medical Nutrition Laboratory, Chicago. 471 pages; 25.5 × 17.5 cm. 1951. The C. V. Mosby Company, Saint Louis. Price, $6.75.

Die Nervenkrankheiten. By PROF. DR. GEORGES SCHALTENBRAND. 880 pages; 25 × 18 cm. 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Ganzleinen DM 87.–

Operative Surgery. 2nd ed. Edited by SIR LANCELOT BARRINGTON-WARD, K.C.V.O., Ch.M., F.R.C.S. (Edin.), F.R.C.S. (Eng.), Surgeon to H. M. King George VI, etc. 638 pages; 25.5 × 17 cm. 1951. Grune & Stratton, New York. Price, $13.50.

Physical Biochemistry. 2nd ed. By HENRY B. BULL, Ph.D., Professor of Chemistry, School of Medicine, Northwestern University. 355 pages; 24 × 15.5 cm. 1951. John Wiley & Sons, Inc., New York. Price, $5.75.

Proceedings of the First Research Conference on Psychosurgery: Criteria for the Selection of Psychotic Patients for Psychosurgery—New York, N. Y., November 17 and 18, 1949. Public Health Service Publication No. 16. Chairman: FRED A. METTLER, M.D., Ph.D.; Editor: NEWTON BIGELOW, M.D. 173 pages; 26 × 20 cm. (paper-bound). 1951. Federal Security Agency, Public Health Service, National Institutes of Health. Price, $1.00—from Superintendent of Documents, Government Printing Office, Washington, D. C.

Proceedings of the Third International Congress of the International Society of Hematology, Cambridge, England—August 21–25, 1950. Editorial Committee: CARL V. MOORE, U.S.A., Editor-in-Chief; L. BERMAN, U.S.A.; J. BERNARD, France; S. HABERMAN, U.S.A.; J. HILL, U.S.A.; H. LÜDIN, Switzerland; R. MACFARLAND, U. K.; S. METTIER, U.S.A.; R. RACE, U. K., and E. STORTI, Italy. 593 pages; 26 × 18 cm. 1951. Grune & Stratton, New York. Price, Cloth bound, $10.00; paper bound, $8.00.

The Public Health Nurse and Her Patient. 2nd ed. By RUTH GILBERT, R.N., Coordinator, Course for Mental Hygiene Consultants and Assistant Professor of Nursing Education, Teachers College, Columbia University. 348 pages; 24.5 × 16 cm. 1951. Published for The Commonwealth Fund by Harvard University Press, Cambridge. Price, $3.75.

The Quantitation of Mixtures of Hemoglobin Derivatives by Photoelectric Spectrophotometry. By FRANCIS T. HUNTER, A.M., M.D., Associate in Medicine, Harvard Medical School, etc. 226 pages; 23.5 × 16 cm. 1951. Charles C. Thomas, Publisher, Springfield, Illinois. Price, $8.50.

Review of Physiological Chemistry. 3d ed. By HAROLD A. HARPER, Ph.D., Professor of Biology (Biochemistry), University of San Francisco, etc. 260 pages; 25.5 × 18 cm. (loose-leaf). 1951. University Medical Publishers, P. O. Box 761, Palo Alto, California. Price, $3.50.

Über die Röntgenologischen Darstellungsmöglichkeiten des Weiblichen Genitalapparates mit Hilfe von Jodöl und Jodsol. By DOZENT DR. MED. HABIL. J. ERBSLÖH. 74 pages; 30.5 × 22 cm. (paper-bound). 1951. Georg Thieme Verlag, Stuttgart; Agents for U. S. A.: Grune & Stratton, Inc., New York. Price, Kartoniert DM 16.80.

COLLEGE NEWS NOTES

The Thirty-Third Annual Session, A.C.P.

The Thirty-third Annual Session of the American College of Physicians, as previously announced, will be held at Cleveland, Ohio, April 21–25, inclusive, 1952, with the General Headquarters at the Municipal Auditorium. While all first-class hotels in Cleveland will be utilized for housing the members, Hotel Statler will be the Headquarters of the Officers, Regents and Governors.

The American Board of Internal Medicine will be conducting oral examinations in Cleveland during the preceding week, and the American Heart Association will be holding its Annual Session at Cleveland also during the previous week. The Housing Bureau of the Cleveland Convention and Visitors' Bureau proposes to use a common hotel reservation form, to be supplied to all physicians who will be taking the examinations of the American Board of Internal Medicine, to all members of the American Heart Association and to all members and guests of the American College of Physicians, thus providing a means of taking care of reservations for the entire period, without doctors having to move from one hotel to another between the different meetings.

The scientific program for the General Sessions and Morning Lectures is in the hands of Dr. Maurice C. Pincoffs, President of the College, University Hospital, Baltimore 1, Md., and local arrangements, along with the program of Clinics and Panel Discussions, are assigned to Dr. Roy W. Scott, General Chairman, 3395 Scranton Road, Cleveland 9, Ohio.

Following the conclusion of the American College of Physicians' convention, a "Mark Twain Cruise" for members of the College and their friends is being planned on the "Delta Queen," leaving Cincinnati on Saturday, April 26, and providing a most interesting and restful cruise to the Kentucky Lakes and return. The cruise ship will return to Cincinnati on Friday, May 2.

A.C.P. Postgraduate Courses

The following Postgraduate Courses on the Autumn Program have been concluded with satisfactory registration, and, in some instances, oversubscription:

No. 1, INTERNAL MEDICINE: SELECTED TOPICS. University of Cincinnati College of Medicine, Cincinnati, Ohio, September 17–21, 1951.

No. 2, INTERNAL MEDICINE: SELECTED SUBJECTS. Marquette University School of Medicine, Milwaukee, Wis., October 8–13, 1951.

No. 3, THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE. Frank E. Bunts Educational Institute of the Cleveland Clinic Foundation, Cleveland, Ohio, October 22–27, 1951.

The following courses are still to be given and, in most instances, registration is still open to members of the College and in some cases to non-members:

No. 4, CLINICAL NEUROLOGY. Jefferson Medical College of Philadelphia, Philadelphia, Pa., October 29–November 2, 1951.

No. 5, ELECTROCARDIOGRAPHY. Emory University School of Medicine, Emory University, Ga., October 29–November 2, 1951.

No. 6, GASTRO–ENTEROLOGY. Tulane University of Louisiana School of Medicine, New Orleans, La., November 12–17, 1951.

No. 7, RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE. Massachusetts General Hospital, Boston, Mass., November 12–17, 1951.

No. 8, CARDIOVASCULAR DISEASES. University of Texas Medical Branch, Galveston, Tex., December 10–15, 1951.

No. 9, PHYSIOLOGICAL BASIS FOR INTERNAL MEDICINE. University of Pennsylvania Graduate School of Medicine, Philadelphia, Pa., December 10–15, 1951.

Course outlines, registration forms and other information should be secured from the Executive Secretary of the College, 4200 Pine Street, Philadelphia 4, Pa.

The Advisory Committee on Postgraduate Courses will meet on November 17, 1951, to make up the roster of Postgraduate Courses to be offered during the first six months of 1952.

Meetings of the Committee on Credentials

The Committee on Credentials of the American College of Physicians will meet next on November 17, 1951. The Board of Regents will meet on November 18, 1951. Proposals for membership in the College, that were received at College Headquarters on or before September 18, 1951, will be considered at this meeting of the Committee. The next meetings of the Committee will be held at Philadelphia in March, 1952, and in Cleveland on April 19, 1952. Proposals for membership to be considered at the March and April meetings must be received at College Headquarters sixty days in advance of said meetings.

New Life Member

The College is gratified to announce that Dr. Benjamin Lane Brock, Orlando, Fla., has become a Life Member of the American College of Physicians since the publication of the last issue of this journal.

A.C.P. Regional Meetings

The North Dakota Regional Meeting was held at Bismarck, September 8, with Dr. Howard Wakefield, F.A.C.P., Governor of the College for Northern Illinois, as special guest and speaker at the Banquet. The meeting was well attended. The program was excellent and there was marked interest. The "Tele-Clinic" moving picture of the highlights of the last Annual Session of the College was shown and was received with enthusiasm.

The Western Pennsylvania Regional Meeting was held at Pittsburgh, September 12, with Dr. T. Grier Miller, F.A.C.P., President-Elect of the College, Philadelphia, and Mr. E. R. Loveland, Executive Secretary, in attendance as speakers at the Banquet. The program was a particularly practical one, the papers given from the standpoint of personal experience of the speakers. More than one hundred were in attendance. Here, too, the "Tele-Clinic" moving picture of the St. Louis Session of the College was shown, and although it was not formally listed on the program and had to be shown at an off hour, more than half remained to see it and expressed great satisfaction and praise for it.

Other Regional Meetings scheduled include:

ARKANSAS–OKLAHOMA, Hot Springs, Ark., September 29, 1951; A. A. Blair, M.D., F.A.C.P., and Wann Langston, M.D., F.A.C.P., Governors; Cyrus C. Sturgis, M.D., F.A.C.P., Ann Arbor, Regent, and Mr. E. R. Loveland, Executive Secretary, official guests.

ARIZONA–NEW MEXICO, Phoenix, Ariz., September 29, 1951; Leslie R. Kober, M.D., F.A.C.P., Governor; Dwight L. Wilbur, M.D., F.A.C.P., San Francisco, Regent, official guest.

WESTERN NEW YORK, Saranac Lake, N. Y., September 29, 1951; Edward C. Reifenstein, Sr., M.D., F.A.C.P., Governor; Maurice C. Pincoffs, M.D., M.A.C.P., Baltimore, President, and Mr. H. K. Canby, Executive Assistant, official guests.

NORTHWEST, Seattle, Wash., October 5–6, 1951; George H. Anderson, M.D., F.A.C.P., Governor for Washington and General Chairman; Mr. E. R. Loveland, Executive Secretary, official guest.

MONTANA–WYOMING, Butte, Mont., October 5–6, 1951; Harold W. Gregg, M.D., F.A.C.P., Governor; Howard P. Lewis, M.D., F.A.C.P., Portland, Ore., Third Vice President, official guest.

MIDWEST, Columbus, Ohio, October 13, 1951; Charles A. Doan, M.D., F.A.C.P., Governor for Ohio and General Chairman; Maurice C. Pincoffs, M.D., M.A.C.P. Baltimore, President; Richard A. Kern, M.D., F.A.C.P., Philadelphia, Secretary-General, and Mr. E. R. Loveland, Executive Secretary, official guests.

NEW ENGLAND, Portland, Maine, October 20, 1951; Richard S. Hawkes, M.D., F.A.C.P., Governor for Maine and General Chairman; Maurice C. Pincoffs, M.D., M.A.C.P., Baltimore, President, official guest.

KENTUCKY, Louisville, October 27, 1951; J. Murray Kinsman, M.D., F.A.C.P., Governor; official guest pending.

NORTHERN CALIFORNIA, San Francisco, Calif., November 2, 1951; Stacy R. Mettier, M.D., F.A.C.P., Governor; Walter L. Palmer, M.D., F.A.C.P., Chicago, Regent, official guest.

SOUTHEASTERN, Jacksonville, Fla., November 2–3, 1951; W. C. Blake, M.D., F.A.C.P., Governor for Florida and General Chairman; Maurice C. Pincoffs, M.D., M.A.C.P., Baltimore, President and Edward L. Bortz, M.D., F.A.C.P., Philadelphia, Regent, official guests.

NEW JERSEY, Newark, November 7, 1951; Edward C. Klein, Jr., M.D., F.A.C.P., Governor; Maurice C. Pincoffs, M.D., M.A.C.P., Baltimore, President, and Mr. E. R. Loveland, Executive Secretary, official guests.

NORTH CAROLINA, Durham, December 6, 1951; Elbert L. Persons, M.D., F.A.C.P., Governor; official guest pending.

In 1952 COLORADO has scheduled its Regional Meeting at Denver, February 12; the MIDSOUTH (Louisiana, Mississippi, Tennessee and Texas) at New Orleans, February 15–16; PUERTO RICO at San Juan, February 17, and KANSAS at Emporia, March 21. Dr. Maurice C. Pincoffs, President, will be the official guest at the Midsouth and Kansas Regional Meetings; Dr. T. Grier Miller, President-Elect, at the Puerto Rico Regional Meeting.

The Fourth Annual Harvard Lecture before the University of Colorado Medical Center, Denver, will be delivered by Dr. William B. Castle, F.A.C.P., Director of the Thorndike Memorial Laboratory and Professor of Medicine at Harvard Medical School, on Friday, November 9, 1951, at 5:00 p.m. Dr. Castle will speak on "Red Cell Destruction in Hemolytic Anemias." The lecture will be given in the Denison Auditorium of the University. Physicians, medical students, nurses and other interested individuals are cordially invited.

The Dallas Southern Clinical Society, in coöperation with the Dallas Internists' Club and the Faculty of the Southwestern Medical School of the University of Texas, will present a Postgraduate Conference in Recent Advances in Diagnosis and Therapy, December 10–12, 1951. Further details may be obtained from the Society at 433 Medical Arts Building, Dallas 1, Tex.

The University of Colorado School of Medicine has announced Postgraduate Courses in Heart Disease and Poliomyelitis to be held during the Fall of 1951. The course on Heart Disease will be held November 15–17, 1951, under the co-sponsorship of the Colorado Heart Association and the Colorado State Department of Public Health. A course on Poliomyelitis will be held December 13–15, 1951, and is planned as a review of the diagnosis and management of patients with poliomyelitis. Inquiries regarding registration, etc., may be made to the Office of the Director of Graduate and Postgraduate Medical Education, 4200 East 9th Avenue, Denver 7, Colo.

Announcement of Van Meter Prize Award

The American Goiter Association again offers the Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The Award will be made at the annual meeting of the Association, which will be held in St. Louis, Mo., May 1, 2 and 3, 1952, provided essays of sufficient merit are presented in competition.

The essays may cover either clinical or research investigations and should not exceed 3000 words in length. They should be presented in English and typewritten, double spaced, and copy, in duplicate, sent to the Corresponding Secretary, Dr. George C. Shivers, 100 E. Saint Vrain St., Colorado Springs, Colo., not later than March 1, 1952. A place will be reserved on the program of the annual meeting of the Association for presentation of the Prize Award Essay by the author, and the essay will be published in the annual Proceedings of the Association.

Heart Association Revises Examination Manual

The American Heart Association has issued the first revision of its manual, "Examination of the Heart." The initial limited printing is being made available free to physicians concerned with the diagnosis of cardiovascular diseases. The purpose of the original booklet was to outline the clinical examination of the heart without the help of any instrument other than the stethoscope. The revision adds new material on blood pressure and comments on the use of the electrocardiograph and other diagnostic procedures employed in heart disease. Requests for the booklet should be directed to local affiliated heart associations or directly to the American Heart Association, 1775 Broadway, New York 9, N. Y.

Ligue Internationale contre le Rhumatisme Year Book

Dr. Robert M. Stecher, F.A.C.P., Cleveland, Ohio, has donated to the College a copy of the Year Book of the Ligue Internationale contre le Rhumatisme, which is a roster of registered rheumatologists throughout the world. Copies of the Year Book may be purchased through Dr. Wm. S. Tegner, Secretary-Treasurer of the Ligue, care of the London Hospital, London 1, England.

Dr. Burgess Lee Gordon Assumes Presidency of the Woman's Medical College of Pennsylvania

Dr. Burgess Lee Gordon, F.A.C.P., medical educator and a foremost authority on diseases of the chest, took office September 1, 1951, as President of the century-old Woman's Medical College of Pennsylvania. Dr. Gordon, who was Clinical Professor of Medicine at Jefferson Medical College of Philadelphia and Director of the Jefferson Hospital's Department for Diseases of the Chest, became the first full-time president of the College.

A native of Spokane, Wash., a graduate of Gonzaga University and of Jefferson Medical College of Philadelphia, Dr. Gordon will succeed Dr. Louise Pearce, a distinguished physician and scientist of Princeton, N. J. For the first time since the Woman's Medical College of Pennsylvania was founded on March 11, 1850, the administrative and academic authority will be centered in a full-time head, Dr. Gordon.

This step was taken in recognition of the increasing complexity of operating a medical college and hospital and of the need for having an administrator to meet the public, to direct fund-raising, to promote greater coöperation with the community and to coördinate the services of the College and Hospital.

Dr. J. Wendell Macleod, F.A.C.P., now of Winnipeg, Man., Canada, has been appointed Dean of the School of Medical Sciences of the University of Saskatchewan, effective July 1, 1952. A University Hospital is being built with a view to extending the medical course from two years to the full program. Dr. Macleod will spend the next year visiting various medical centers with the aid of grants to the University from the Rockefeller Foundation and the Commonwealth Fund.

Among the guest speakers at the Clinical Congress of the Connecticut State Medical Association and the Yale University School of Medicine which was held in New Haven, Conn., September 11–13, were Dr. Thaddeus S. Danowski, F.A.C.P., Pittsburgh, Pa., "Uses of Resins in Treatment of Edema"; Dr. Charles K. Friedberg, F.A.C.P., New York, N. Y., "Treatment of Anuria"; Dr. Maxwell Finland, F.A.C.P., Boston, Mass., "Uses and Abuses of Antibiotics."

Dr. Eugene H. Drake, F.A.C.P., Portland, Maine, was named President-Elect of the Maine Medical Association at its annual meeting last June.

At the 27th Annual Meeting of the American College of Radiology held in Atlantic City, N. J., on June 10, the Degree of Fellow of the American College of Radiology was conferred upon Dr. Howard J. Hutter (Associate), Huntington, N. Y., Dr. George Jay Baylin (Associate), Durham, N. C., and Dr. Sydney E. Johnson, F.A.C.P., Louisville, Ky.

Dr. Maxwell M. Wintrobe, F.A.C.P., Salt Lake City, Utah, was among the guest speakers at the annual session of the Colorado State Medical Society held in Denver, September 18–21. His subject was "Diagnosis and Treatment of Anemia."

The State University of Iowa College of Medicine has announced the promotion of Dr. Henry E. Hamilton (Associate), Iowa City, to the rank of Assistant Professor in the Department of Internal Medicine.

Dr. William P. Boger, F.A.C.P., Philadelphia, Pa., was recently appointed Medical Director of Sharp & Dohme, Inc. Dr. Boger has been connected with this pharmaceutical manufacturer since 1945.

Dr. Hugh H. Hussey, Jr., F.A.C.P., Associate Professor of Medicine at Georgetown University School of Medicine, has been appointed Associate Editor of *"GP,"* published by the American Academy of General Practice.

Dr. Oscar Swineford, Jr., F.A.C.P., Charlottesville, Va., addressed the West Virginia State Medical Association on "The Role of the Practitioner in the Management of Asthma" and the West Virginia Academy of Ophthalmology and Otolaryngology on "The Use of ACTH and Cortisone in Ophthalmology and Otolaryngology" at their annual meetings in White Sulphur Springs, July 20.

Dr. Frank L. Roberts, F.A.C.P., Assistant Dean and Professor of Preventive Medicine at the University of Tennessee College of Medicine, was recently honored by the West Tennessee Public Health Co-workers Council for his contributions to public health. Following a dinner, the organization of public health workers presented a plaque to Dr. Roberts.

Dr. Carroll L. Birch, F.A.C.P., Professor of Medicine at the University of Illinois College of Medicine, has been appointed Dean of the Lady Hardinge Medical College for Women at New Delhi, India, for one year. This college is the only Indian medical institution for the training of women. Dr. Birch's assignment will be to train a replacement to take over the duties of Dean and to prepare recommendations for the reorganization of teaching methods and curricula to raise school standards to meet those of modern medical educational institutions.

Dr. Charles S. Davidson, F.A.C.P., Associate Director of the Thorndike Memorial Laboratory, Boston, Mass., was recently appointed Chief of the Clinical Investigations Branch of the National Institute of Arthritis and Metabolic Disease.

The American Therapeutic Society has announced that its officers for the year 1951–52 include Dr. Wendell B. Gordan (Associate), Pittsburgh, Pa., President; Dr. Oscar B. Hunter, F.A.C.P., Washington, D.C., Secretary; and Dr. Howard Wakefield, F.A.C.P., Chicago, College Governor for Northern Illinois, Treasurer.

Dr. Alphonse McMahon, F.A.C.P., Associate Professor of Internal Medicine, St. Louis University School of Medicine, was recently named Chief of Staff of St. John's Hospital, St. Louis, Mo.

Dr. Robert H. Williams, F.A.C.P., Seattle, Wash., spoke on "Adrenal Physiology and Therapy" at the Annual Session of the Montana Medical Association held in Great Falls, September 13–16.

Among the speakers at the Annual Session of the Utah State Medical Association held in Salt Lake City, September 13–15, were Dr. Laurance W. Kinsell, F.A.C.P., Oakland, Calif., "Present Status of the Clinical Application of ACTH and Cortisone"; and Dr. Arthur C. Curtis, F.A.C.P., Ann Arbor, Mich., "Cutaneous Lesions as a Manifestation of Systemic Disease."

Nine Fellows of the College were among the guest speakers at the Graduate Fortnight of the New York Academy of Medicine, under the general subject, "Disorders of the Circulatory System," which was held in coöperation with The New York Heart Association, October 8–19. They were: Dr. Herrman L. Blumgart, Boston, Mass., "Coronary Disease: Clinical-Pathologic Correlations and Physiology"; Dr. Robert L. Levy, New York, N. Y., "The Clinical Recognition of Coronary Heart Disease"; Dr. William Dock, Brooklyn, N. Y., "Mechanism and Management of Circulatory Failure"; Dr. Lewis Dexter, Boston, Mass., "Dynamics of Acquired Valve Lesions"; Dr. Eugene A. Stead, Jr., Durham, N. C., "Edema and Dyspnea of Heart Failure"; Dr. Louis N. Katz, Chicago, Ill., "The Importance of Cardiac Arrhythmias"; Dr. A. Wilbur Duryee, New York, N. Y., "The Medical Management of Acute and Chronic Arterial Occlusion"; and Dr. Charles E. Kossman, New York, N. Y., "Electrocardiographic Evidence of Pericardial and Myocardial Injury."

Dr. Hugh Montgomery, F.A.C.P., and Dr. O. Spurgeon English, F.A.C.P., both of Philadelphia, were among the guest speakers at the Annual Meeting of the Medical Society of Delaware, held in Wilmington, October 8–10.

The University of Pennsylvania Graduate School of Medicine has announced the following promotions in its faculty:

Dr. Joseph F. Hughes, F.A.C.P., from Assistant Professor to Associate Professor of Experimental Neurology;

Dr. Merle M. Miller, F.A.C.P., from Assistant Professor to Associate Professor of Allergy;

Dr. Thomas M. McMillan, F.A.C.P., College Governor for Eastern Pennsylvania, from Associate Professor to Professor of Clinical Cardiology;

Dr. Pierre C. Simonart (Associate), from Associate to Assistant Professor of Psychiatry.

Dr. Julius H. Comroe, Jr., F.A.C.P., Professor of Physiology and Pharmacology at the University of Pennsylvania Graduate School of Medicine, was recently appointed a member of the Subcommittee on Thoracic Surgery, National Research Council.

Dr. David A. Cooper, F.A.C.P., Associate Professor of Medicine at the University of Pennsylvania Graduate School of Medicine, is President-Elect of the American Trudeau Society, the Medical Branch of the National Tuberculosis Association.

Six Fellows of the American College of Physicians were among the guest speakers at the Annual Session of the Medical Society of the State of Pennsylvania, which was held at Pittsburgh, September 16–20. They were Dr. Everett N. Collins, Dr.

A. Carlton Ernstene, and Dr. Irvine H. Page, all of Cleveland, Ohio, Dr. Richard H. Freyberg, New York, N. Y., Dr. Thomas H. Ham, Boston, Mass., and Dr. Cyril M. MacBryde, St. Louis, Mo.

Dr. Anton J. Carlson, M.A.C.P., Professor Emeritus of Physiology at the University of Chicago School of Medicine, was recently elected President of the Illinois Society for Medical Research. At the same time, Dr. Andrew C. Ivy, F.A.C.P., Vice-President and Head of the Professional Colleges, University of Illinois, was elected Vice-President.

Among the guest speakers at the Annual Meeting of the Michigan State Medical Society, which was held in Grand Rapids, September 26–28, were Dr. Sara M. Jordan, F.A.C.P., Boston, Mass., "Peptic Ulcer, Complications and Treatment"; Dr. Richard V. Ebert, F.A.C.P., Minneapolis, Minn., "Differentiation of Dyspnea Caused by Cardiac Disease from Dyspnea Associated with Pulmonary Emphysema"; and Dr. Elmer L. Sevringhaus, F.A.C.P., Nutley, N. J., "Vitamin Therapy in Clinical Practice."

Dr. O. Spurgeon English, F.A.C.P., Philadelphia, Pa., and Dr. Frank H. Bethell, F.A.C.P., Ann Arbor, Mich., were among the guest speakers at the Annual Meeting of the State Medical Society of Wisconsin, which was held in Milwaukee, October 1–3. Dr. Bethell's subject was "Treatment of Anemia," and Dr. English spoke on "A Treatment Plan for Psychosomatic Illness."

At the joint Annual Meeting of the New Hampshire and Vermont state medical societies, which was held in Manchester, Vt., September 30 through October 2, Dr. John S. L. Browne, F.A.C.P., Montreal, Canada, spoke on "Basic Considerations in the Use of ACTH and Cortisone," and Dr. Chester S. Keefer, F.A.C.P., Boston, Mass., spoke on "Present Day Evaluation of Antibiotics."

OBITUARIES

DR. JAMES E. PAULLIN

Dr. James Edgar Paullin, Master and former President of the American College of Physicians, died in Piedmont Hospital on August 13, 1951, at 6:00 p.m. Five hours before, while examining a patient in his office, he was seized with severe chest pain. Even in his own final illness he demonstrated his remarkable ability as a clinician. He made his own diagnosis of rupture of the mid portion of the thoracic aorta. The end was sudden and quiet. The surrounding circumstances were as he wished, while working with patients, among his friends and with his family. The day prior to his passing he had returned from a pleasant vacation with his family and lifelong friend, Dr. James S. McLester.

The disease that caused his death had been of particular interest to him for many years. In 1937 he contributed a publication on this subject in the Journal of the American Medical Association.

Born at Fort Gaines, Georgia, on November 3, 1881, he was the son of Edgar Paullin, Sr., and Leola Wiggins Paullin. His preliminary education was received in Fort Gaines High School and the John Gibson Institute from which he graduated in 1897. He then attended Mercer University in Macon, Georgia. There his first interest in medicine was stimulated by his professor of chemistry, Dr. James F. Sellers. Following his graduation with an A.B. degree he remained at Mercer for a year of postgraduate work in the sciences before entering medical school at Johns Hopkins University from which he graduated in 1905.

On December 17, 1908, he married Edna Louise Frederick of Marshallville, Georgia, who survives him. Their daughter, Caroline, is the wife of Dr. William R. Minnich who was associated with him in the practice of medicine.

Following an internship at the Rhode Island General Hospital he spent a year at the Piedmont Hospital before beginning practice in Atlanta in 1907. He immediately set about to improve the medical facilities of his community by setting up facilities for carrying out the Wassermann test. He was active in the State Health Department and a worker in the Pasteur Institute. He was the first physician in the state to use insulin and to advocate the adequate caloric feeding of typhoid patients who prior to that time were treated on a starvation regimen. He wrote the first comprehensive report on typhus fever in Georgia.

Soon after beginning practice he associated himself with medical education and progressed from lecturer in histology, pathology and bacteriology to adjunct professor of medicine of the Atlanta Medical College. In 1915 this school became the Emory University School of Medicine and Dr. Paullin was named Clinical Professor of Medicine. This position he held until he retired from the active faculty in 1950. During this time he won the admiration and respect of thirty-five graduating classes. These former students together with other friends expressed their appreciation of his

efforts by the establishment of the James Edgar Paullin Scholarship Fund in 1950. It was his pleasure to see the first student award of this scholarship in May 1951. The example set by his own professor, Sir William Osler, was emulated throughout his years of teaching. He would usually present each member of the graduating class a copy of Sir William Osler's "A Way of Life." His long and faithful service as a teacher was characterized by punctuality of attendance, exactness of knowledge and clearness of exposition. His ability to conduct clinicopathological conferences was unexcelled, and he remained the keen diagnostician to the end. Dr. Paullin's patients felt his warm personality and deep interest in their problems. Because both patients and physicians recognized these qualities, his practice was large and he was much in demand as a consultant.

His contributions to the medical literature gave evidence of his ability as clinical investigator as well as teacher and physician. He was the author of more than fifty scientific articles from 1908 to 1950. Bacteriology, pathology, diabetes mellitus, syphilis, cardiovascular disease and medical education were the subjects of most of these publications.

Dr. Paullin's interest in organized medicine began with his county medical society and continued with such interest and ability that as a result he became President of the Fulton County Medical Society, the State Medical Association of Georgia, the American College of Physicians, the American Medical Association, and the Association of American Physicians.

His military record was characterized by an untiring effort in the service of his country. In World War I he was a major and Chief of Medical Service at Camp Shelby, Mississippi. During World War II he was Honorary Consultant to the Surgeon General of the United States Navy and visited the medical installations of the Far Eastern Command. His classification of physicians for the Procurement and Assignment Agency was a most valuable contribution in the early phase of the war. For his service in World War II he was awarded the nation's highest civilian award, the President's Medal of Merit, in 1947.

His contribution as a citizen of his community was recognized by the Atlanta Chamber of Commerce in 1944 when he received the Certificate for Distinguished Achievement.

Dr. Paullin became a Fellow of the American College of Physicians in 1928. His interest and effort for the College increased each year. In 1935 he became a member of the Board of Regents, and was President-elect and President from 1941–1944. He was made a Master of the College in 1947, and in 1950 was awarded the Alfred Stengel Memorial diploma for service to the College and eminence in the field of medicine.

Only a full biography could adequately record the accomplishments of this great physician.

Following are additional offices, honors and affiliations that served to fill his life to the fullest: A member of the Presbyterian church, Sigma Nu Social Fraternity, Phi Chi Medical Fraternity, Alpha Omega Alpha Honorary Medical Fraternity; LL.D. degrees from Emory University and Mercer University; diplomate of the American Board of Internal Medicine; chairman of Section on Practice of Medicine of the A.M.A., 1928; member of the Council on Scientific Assembly, 1933–1942; president of the American Clinical and Climatological Society, 1937; president of the Interstate Postgraduate Medical Association, 1946–7; chairman of the Medical Section of the Southern Medical Association; corresponding member of the Society of Internal Medicine, Buenos Aires; member of the Medical Board of the National Foundation for Infantile Paralysis; guest professor of Medicine, Peter Bent Brigham Hospital, Boston, and of Pratt Diagnostic Clinic; member of National Research Council; participant in Finlay Institute of the Americas for Interchange of Medical Science with Latin American Countries; decorated with Order of Carlos Finlay by

President Bastista of Cuba, 1942; member of the Federal Hospital Council of U. S. Public Health Service; consultant for Council on National Emergency Medical Service; personal physician to the late President Franklin D. Roosevelt and attended him at the time of his death in 1945 at Warm Springs, Georgia; visiting physician, Grady Memorial Hospital and Piedmont Hospital.

From a study of Dr. Paullin's life one can learn to be a better citizen and physician. He will be greatly missed by his family, friends and associates but the stimulating effect of his warm personality and brilliant intellect will be felt for many years to come.

CARTER SMITH, M.D., F.A.C.P.,
Governor for Georgia

DR. WILLIAM DE BERNIERE MACNIDER

In recording the death, on May 31, 1951, of Dr. William de Berniere MacNider, F.A.C.P., the Editor of the *North Carolina Medical Journal* wrote:

"Dr. MacNider began his teaching career at the University of North Carolina while he was still an undergraduate student. This was quite in keeping with his character, for all the rest of his life he continued to be both a teacher and a student. He was almost certainly the most famous medical man that North Carolina ever produced. His research made him an international authority on the kidney. The long list of his achievements in *Who's Who* is evidence of the wide recognition given him at home and abroad. Although he walked with the kings of medicine, . . . he never lost the common touch. His capacity for friendship seemed unlimited."

Dr. MacNider was born in Chapel Hill, the seat of the University of North Carolina, June 25, 1881. His high school and college work, and his medical course were completed there, during the brief life of the four-year Medical School of the University. After receiving the M.D. in 1903 he did postgraduate work in Pharmacology at the University of Chicago and at Western Reserve University. In 1905 he established the first Department of Pharmacology in the South, at the University of North Carolina.

In 1918, when Kenan Professorships were established, Dr. MacNider was one of the first three professors accorded this special honor. From 1937 to 1940 he served as Dean of the two-year Medical School of the University of North Carolina. In 1943 he resigned as Head of the Department of Pharmacology and assumed the title of Kenan Research Professor of Pharmacology which he held until he became emeritus in 1950.

Dr. MacNider became a Fellow of the American College of Physicians in 1925, and he recalled what might be regarded as the first North Carolina Regional Meeting of the College, a luncheon, at Wrightsville Beach, N. C., during the 1925 Meeting of the North Carolina State Medical Society, when he was the President. His interest in the College continued, and he attended both informal and formal meetings, which were held in various cities after 1928. At the 1950 Meeting at Chapel Hill, his presence as an honored guest was a factor in an attendance of more than one hundred physicians.

Among numerous honors and evidences of recognition of Dr. MacNider's work may be mentioned: the Gibbs Prize of the New York Academy of Medicine in 1931, the Research Medal of the Southern Medical Association in 1933, honorary Doctor of Science, Medical College of Virginia, 1933, and Doctor of Laws, Davidson College, 1934. He was awarded the George M. Kober Medal of the Association of American Physicians in 1941, having been elected to the Association in 1921. He was Harvey Society lecturer, 1928–29, and made the Annual Convocation Address of the American College of Physicians at the Annual Session at St. Paul, Minnesota, in 1942, on "A Consideration of the Factor of Change in the Animal Organism."

Although few men in his situation have achieved such prominence in research, Dr. MacNider's greatest contribution was to the improvement of medical education, particularly in North Carolina. His unswerving loyalty to his own Alma Mater helped to maintain the high standard of its two-year medical school which has made possible its expansion into a four-year school, realizing Dr. MacNider's life-long dream. He was always active in the development of Watts Hospital in Durham, serving as an honorary consultant for many years, and he gave, unstintingly, from his experience and wisdom, in assisting the foundation and early development of the Duke University School of Medicine, including regular lectures in Pharmacology in the early nineteen thirties.

Dr. MacNider never lost the faculty of establishing warm and inspiring personal relationships with students. In the Spring of 1951 the second year class of the University of North Carolina Medical School presented to the school the William deB. MacNider Award for "public commendation of a sophomore medical student who is to be elected by classmates as possessing the intangible traits of good character, which have been typified by Dr. 'Billy' MacNider during his 51 years as teacher and physician in the University."

ELBERT L. PERSONS, M.D., F.A.C.P.,
Governor for North Carolina

DR. HAROLD EDWARD RICHARDSON, SR.

Harold Edward Richardson, Sr., B.S., M.D., F.A.C.P., was born February 17, 1895, at Steven's Point, Wis., son of Herbert Nelson and Johanna Angela (Linneman) Richardson. His mother was the first white child born in Stearns County, Minn.—in 1857. At the University of Minnesota he received the degrees of B.S. in 1917, M.B. in 1919 and M.D. in 1920. In 1919 he married Clarissa May Clay, M.D. (deceased 1933), and in 1937 Margaret Horsch Kiesner.

He began his active medical career as Deputy Coroner of Hennepin County in 1918, and after his internship became associated with Dr. Charles Lyman Greene of St. Paul from 1920 to 1926. He served as Head of the Medical Department, St. Paul Clinic 1927–37 and since 1937 has been in private practice in Internal Medicine and Cardiology. He served on the Staff of St. Joseph's, Miller and St. Luke's Hospitals and was Consultant at the Gillette State Hospital for Crippled Children. Dr. Richardson was a Diplomate of the American Board of Internal Medicine, a Fellow of the American Medical Association, a Member of the State and County Medical Societies and many other organizations dealing with medicine and allied interests, and was also a Fourth Degree Member of the Knights of Columbus. He had been a Life Member of the College since 1948.

During World War I he enlisted in the Medical Reserve Corps in 1917. He has served as Medical Examiner in Board 11, Ramsey County, Selective Service since 1941. He served as Clinical Instructor in Medicine at the University of Minnesota Medical School and on the Medical Staff of Ancker Hospital in St. Paul. His publications on electrocardiography, cardiac-neurosis and clinical recognition of coronary disease were important and well received.

He was held in the highest esteem by his colleagues in the Twin Cities, the State and the Northwest, and will be greatly missed by them and by many patients to whom he endeared himself by his keen interest, sterling worth and unremitting zeal.

Plagued for five years, first by recurring episodes of pericarditis, and later by angina pectoris, he nevertheless carried on with courage and devotion to the high ideals which animated him. He died June 18, 1951, from coronary occlusion, aged 56.

S. MARX WHITE, M.D., F.A.C.P.